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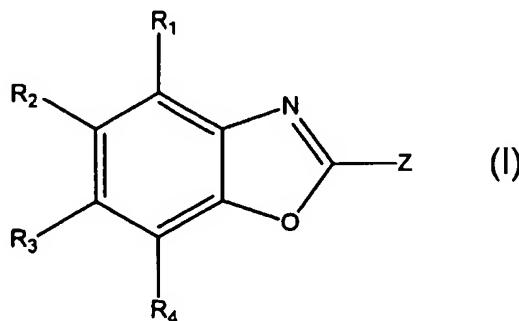
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(54) Title: 2-AMINOBENZOXAZOLE DERIVATIVES AND COMBINATORIAL LIBRARIES THEREOF

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(57) Abstract: The present invention relates to novel 2-aminobenzoxazole derivative compounds of the following formula (I), wherein R₁ to R₄ and Z have the meanings provided herein. The invention further relates to combinatorial libraries containing two or more such compounds, as well as methods of preparing 2-aminobenzoxazole derivative compounds.

2-AMINOBENZOXAZOLE DERIVATIVES
AND COMBINATORIAL LIBRARIES THEREOF

BACKGROUND OF THE INVENTION

5

FIELD OF THE INVENTION

The present invention relates generally to the synthesis of compounds comprising heterocyclic rings. In 10 one embodiment, the invention provides novel 2-aminobenzoxazole derivative compounds as well as novel combinatorial libraries comprised of such compounds.

BACKGROUND INFORMATION

15

The process of discovering new therapeutically active compounds for a given indication involves the screening of all compounds from available compound collections. From the compounds tested, one or more 20 structures is selected as a promising lead. A large number of related analogs are then synthesized in order to develop a structure-activity relationship and select one or more optimal compounds. With traditional "one-at-a-time" synthesis and biological testing of analogs, this 25 optimization process is long and labor intensive. Adding significant numbers of new structures to the compound collections used in the initial screening step of the discovery and optimization process cannot be accomplished with traditional "one-at-a-time" synthesis methods, 30 except over a time frame of years or even decades. Faster methods are needed that allow for the preparation of up to thousands of related compounds in a matter of days or a few weeks. This need is particularly evident

when synthesizing more complex compounds, such as 2-aminobenzoxazole derivatives.

Benzoxazoles and related derivative compounds 5 have been the subject of investigation in a number of different biological areas. For example, such compounds have been proposed or used as 5-HT₃ antagonists, 5-HT₃ agonists or 5-HT₄ (5-hydroxytryptamine, or seotonin) agonists (Monge et al., *J. Med. Chem.*, 37:1320 (1994) and 10 Yasao et al., *J. Med. Chem.*, 41:3015 (1998); as antihistamines (Hong et al., *Tetr. Lett.*, 38:5607 (1997); and as immunological agents (St. Gorgiev et al., *Eur. J. Med. Chem.*, 24:639-41 (1989).

15 Benzoxazole derivatives have long been the subject of serial chemical synthesis. See, for example, Iwamatsu et al., U.S. Pat. No. 5,631,257; Bowles et al., U.S. Pat. No. 5,206,366; De Nanteuil et al., 6,040,327; Griffin et al., 6,015,827; De Nanteuil et al., 5,972,968; 20 Bradbury et al., U.S. Pat. 5,387,592; Poss et al., U.S. Pat. No. 5,190,942; Arrowsmith et al., U.S. Pat. No. 5,158,964; Iijima et al., U.S. Pat. No. 4,948,900; Iijima et al., U.S. Pat. No. 4,897,393; Saitoh et al., U.S. Pat. No. 4,728,612; Saitoh et al., 4,690,926; Dawson et al., 25 U.S. Pat. No. 4,416,892; Chu-Moyer et al., *J. Org. Chem.*, 60:5721 (1995); Lok et al., *J. Org. Chem.*, 61:3289 (1996); and Kover et al., *Synthesis*, 1124 (1994).

Benzoxazole derivative synthesis has even been 30 extended to combinatorial chemical methods. Wang et al., *Tetr. Lett.*, 38:6529 (1997). However, the libraries to date contain compounds of limited diversity and complexity. Indeed, more complex benzoxazole

derivatives, especially those amino substituted at the 2-position, have been difficult to attain.

A need therefore exists to develop more complex
5 libraries based on heterocyclic medicinal compounds that
would need less time and effort in the synthesis and
testing required to bring an organic pharmaceutical
product to fruition. In short, improved methods for
generating therapeutically useful heterocyclic compounds,
10 such as 2-aminobenzoxazole derivatives, are desired.

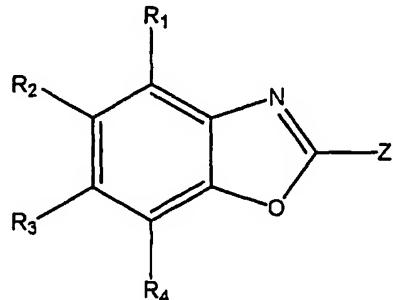
This invention satisfies this need and provides
related advantages as well. The present invention
overcomes the known limitations of classical serial
15 organic synthesis of 2-aminobenzoxazole derivatives, for
example, as well as the shortcomings of combinatorial
chemistry related to 2-aminobenzoxazole derivatives. The
present invention allows for rapid generation of large
diverse libraries of complex 2-aminobenzoxazole
20 derivatives as discrete molecules.

The present invention can utilize a readily
available pool of building blocks that can be
incorporated into the various regions of the molecule.
25 Furthermore, the method of making the present invention
allows for the use of building blocks that contain a wide
range of diverse functionality. Such building blocks can
provide combinatorial libraries that consist of large
numbers as well as combinatorial libraries that are
30 extremely diverse with respect to the functionality
contained within those libraries. The present invention
combines the techniques of solid-phase synthesis of 2-
aminobenzoxazole derivatives and the general techniques

of synthesis of combinatorial libraries to prepare highly diverse new 2-aminobenzoxazole derivative compounds.

SUMMARY OF THE INVENTION

The present invention relates to novel 2-aminobenzoxazole derivative compounds of the following formula:



wherein R₁ to R₄ and Z have the meanings provided herein.

The invention further relates to combinatorial libraries containing two or more such compounds, as well 15 as methods of preparing 2-aminobenzoxazole derivative compounds.

BRIEF DESCRIPTION OF THE DRAWINGS

20 Figure 1 shows a reaction scheme for the combinatorial synthesis of 2-aminobenzoxazole derivative compounds, showing Z of the claimed invention as Formula A. In step 1, R₁-NH₂ is added in the presence of NaBH₃CN and DMF/1% HOAc (noting that R₁ of this Figure 25 corresponds to R¹¹ or R¹² of the claimed invention). In step 2, carboxy-2-(methylthio)-1,3-benzoxazole is added in the presence of DIC and HOBT. In step 3, a diamine is

added in the presence of DMSO at 75°C (noting that R₃ of the Figure corresponds to R₅ of the claimed invention, and R of the Figure corresponds to R₆ and R₇ of the claimed invention. In step 4, R₄CO₂H or R₄SO₂Cl is added (noting 5 that X of the Figure and claimed invention includes carbonyl and sulfonyl, and that R₄ of the Figure corresponds to R₈ of the claimed invention.

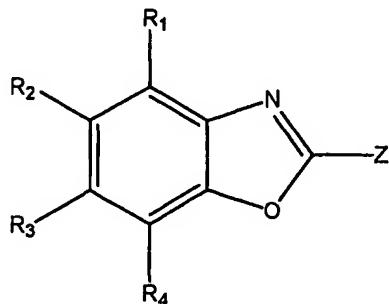
Figure 2 shows a similar reaction scheme as 10 Figure 1, except showing a different resin-attached starting material.

Figure 3 shows a reaction scheme for the combinatorial synthesis of 2-aminobenzoxazole derivative 15 compounds, showing Z of the claimed invention as Formula B. The reagents, materials and conditions are similar to those of Figure 1, as described above, except that, in step 3, an amino alcohol is added in the presence of N,N-dimethylacetamide and 20 tetramethylguanidine at 73° C (noting that R₃ of the Figure corresponds to the nitrogen heteroatom and R₅ of Forumla b of the claimed invention, and R₄ of the Figure corresponds to R₈ and R₉ of the claimed invention).

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds and combinatorial libraries of compounds of the formula:

5

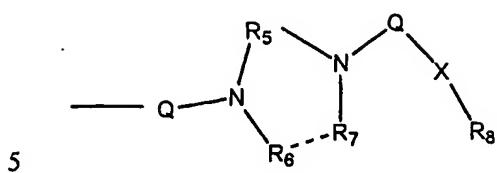


where R₁ and R₄, and one of R₂ and R₃, are independently a
 10 hydrogen atom, halo, hydroxy, protected hydroxy, cyano, C₁ to C₁₂ alkyl, C₂ to C₁₂ alkenyl, C₂ to C₁₂ alkynyl, C₁ to C₁₂ substituted alkyl, C₂ to C₁₂ substituted alkenyl, C₂ to C₁₂ substituted alkynyl, C₁ to C₁₂ alkoxy, C₁ to C₁₂ substituted alkoxy, C₁ to C₁₂ acyloxy, C₁ to C₁₂ acyl, C₃ to
 15 C₇ cycloalkyl, C₃ to C₇ substituted cycloalkyl, C₅ to C₇ cycloalkenyl, C₅ to C₇ substituted cycloalkenyl, heterocyclic ring, substituted heterocyclic ring, C₇ to C₁₈ phenylalkyl, C₇ to C₁₈ substituted phenylalkyl, C₁ to C₁₂ heterocycloalkyl, C₁ to C₁₂ substituted
 20 heterocycloalkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, cyclic C₂ to C₇ alkylene, substituted cyclic C₂ to C₇ alkylene, cyclic C₂ to C₇ heteroalkylene, substituted cyclic C₂ to C₇ heteroalkylene, carboxy, protected carboxy,
 25 hydroxymethyl, protected hydroxymethyl, protected amino, protected (monosubstituted)amino, (disubstituted)amino, C₁ to C₁₀ alkyl protected amino, C₁ to C₁₀ alkyl protected (monosubstituted)amino, C₁ to C₁₀

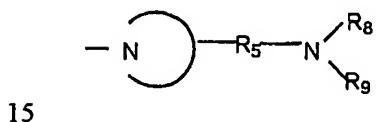
alkyl(disubstituted)amino, C₁ to C₁₀ substituted
alkylamino, C₁ to C₁₀ substituted alkyl protected
(monosubstituted)amino, C₁ to C₁₀ substituted
alkyl(disubstituted)amino, carboxamide, C₁ to C₁₀
5 alkylthio, C₁ to C₁₀ substituted alkylthio, C₁ to C₁₀
alkylsulfonyl, C₁ to C₁₀ substituted alkylsulfonyl, C₁ to
C₁₀ alkylsulfoxide, C₁ to C₁₀ substituted alkylsulfoxide,
phenylthio, substituted phenylthio, phenylsulfoxide,
substituted phenylsulfoxide, phenylsulfonyl, substituted
10 phenylsulfonyl, (i) the formula -C(O)NR¹¹R¹², (ii) the
formula -SR¹¹, (iii) the formula -OR¹¹ or (iv) the formula
-C(O)OR¹¹, wherein R¹¹ and R¹² are, independently, a
hydrogen atom, C₁ to C₁₂ alkyl, C₁ to C₁₂ substituted
alkyl, C₂ to C₁₂ alkenyl, C₂ to C₁₂ substituted alkenyl,
15 phenyl, substituted phenyl, naphthyl, substituted
naphthyl, C₇ to C₁₈ phenylalkyl, C₇ to C₁₈ substituted
phenylalkyl, C₁ to C₁₂ heterocycloalkyl, C₁ to C₁₂
substituted heterocycloalkyl, heteroaryl, substituted
heteroaryl, heterocycle or substituted heterocycle;
20
the other of R₂ and R₃ is a hydrogen atom, halo, hydroxy,
protected hydroxy, carboxy, thio, C₁ to C₁₂ alkyl, C₂ to
C₁₂ alkenyl, C₂ to C₁₂ alkynyl, C₁ to C₁₂ substituted alkyl,
C₂ to C₁₂ substituted alkenyl, C₂ to C₁₂ substituted
25 alkynyl, C₁ to C₁₂ alkoxy, C₁ to C₁₂ substituted alkoxy, C₁
to C₁₂ acyloxy, C₁ to C₁₂ acyl, C₃ to C₇ cycloalkyl, C₃ to
C₇ substituted cycloalkyl, C₅ to C₇ cycloalkenyl, C₅ to C₇
substituted cycloalkenyl, heterocyclic ring, substituted
heterocyclic ring, C₇ to C₁₈ phenylalkyl, C₇ to C₁₈
30 substituted phenylalkyl, C₁ to C₁₂ heterocycloalkyl, C₁ to
C₁₂ substituted heterocycloalkyl, phenyl, substituted
phenyl, naphthyl, substituted naphthyl, cyclic C₂ to C₇
alkylene, substituted cyclic C₂ to C₇ alkylene, cyclic C₂

to C₇ heteroalkylene, substituted cyclic C₂ to C₇ heteroalkylene, carboxy, protected carboxy, hydroxymethyl, protected hydroxymethyl, protected amino, protected (monosubstituted) amino, (disubstituted) amino, C₁ to C₁₀ alkyl protected amino, C₁ to C₁₀ alkyl protected (monosubstituted) amino, C₁ to C₁₀ alkyl (disubstituted) amino, C₁ to C₁₀ substituted alkyl protected amino, C₁ to C₁₀ substituted alkyl protected (monosubstituted) amino, C₁ to C₁₀ substituted alkyl (disubstituted) amino, C₁ to C₁₀ substituted alkylthio, C₁ to C₁₀ substituted alkylsulfonyl, C₁ to C₁₀ substituted alkylsulfoxide, C₁ to C₁₀ substituted phenylthio, substituted phenylthio, phenylsulfoxide, substituted phenylsulfoxide, phenylsulfonyl, substituted phenylsulfonyl, (i) the formula -C(O)NR¹¹R¹², (ii) the formula -SR¹¹, (iii) the formula -OR¹¹, (iv) the formula -C(O)OR¹¹ or (v) the formula S(O)₂NR¹¹R¹², wherein R¹¹ and R¹² are, independently, a hydrogen atom, C₁ to C₁₂ alkyl, C₁ to C₁₂ substituted alkyl, C₂ to C₁₂ alkenyl, C₂ to C₁₂ substituted alkenyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C₇ to C₁₈ phenylalkyl, C₇ to C₁₈ substituted phenylalkyl, C₁ to C₁₂ heterocycloalkyl, C₁ to C₁₂ substituted heterocycloalkyl, heteroaryl, substituted heteroaryl, heterocycle or substituted heterocycle;

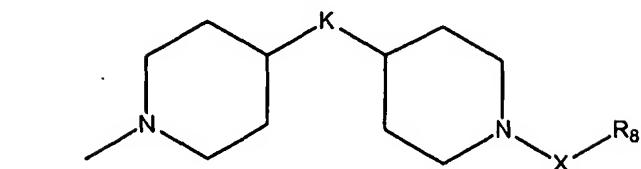
Z is the structure A:



10 or the structure B:



20 or the structure C:



30 where, in structure A, Q is the formula $((\text{CH}_2)_n\text{NH})_m$, where m is 0 or 1, n is 1 to 6 and the alkylene portion of Q is directly attached to the depicted nitrogen atom in structure A; and the dotted line between R₆ and R₇ indicates that R₆ and R₇ are optionally directly attached;

where, in structure B, the depicted cyclic portion is an unsubstituted or substituted heterocycle that is fully saturated, contains 4 to 7 ring atoms, 1 to 2 nitrogen

rings atoms and 0 to 1 other heteroatoms selected from oxygen and sulfur;

where, in structure C, K is absent or present and, if 5 present, is a C₁ to C₁₂ alkylene;

R₅ is C₁ to C₁₀ alkylene, C₂ to C₁₀ alkenylene, C₂ to C₁₀ alkynylene, C₁ to C₁₀ substituted alkylene, C₂ to C₁₀ substituted alkenylene, C₂ to C₁₀ substituted alkynylene, 10 substituted epimino, C₁ to C₅ substituted alkylene epimino, thio, C₁ to C₁₀ alkylene thio, C₁ to C₁₀ substituted alkylene thio, sulfonyl, C₁ to C₁₀ alkylene sulfonyl, C₁ to C₁₀ substituted alkylene sulfonyl, sulfinyl, C₁ to C₁₀ alkylene sulfinyl, C₁ to C₁₀ substituted alkylene sulfinyl, oxy, C₁ to C₁₀ alkylene oxy, C₁ to C₁₀ alkylene dioxy, C₁ to C₁₀ substituted alkylene dioxy, C₁ to C₁₀ alkylene trioxy or C₁ to C₁₀ substituted alkylene trioxy; 15

20 X is absent or present and, if present, is carbonyl, thiocarbonyl, thioester, sulfonyl and sulfinyl; and where R₆ and R₇ are not directly attached to each other, they are, independently, a hydrogen atom, C₁ to C₁₂ alkyl, 25 C₂ to C₁₂ alkenyl, C₂ to C₁₂ alkynyl, C₁ to C₁₂ substituted alkyl, C₂ to C₁₂ substituted alkenyl, C₂ to C₁₂ substituted alkynyl, C₃ to C₇ cycloalkyl, C₃ to C₇ substituted cycloalkyl, C₅ to C₇ cycloalkenyl, C₅ to C₇ substituted cycloalkenyl, heterocyclic ring, substituted heterocyclic 30 ring, C₇ to C₁₈ phenylalkyl, C₇ to C₁₈ substituted phenylalkyl, C₁ to C₁₂ heterocycloalkyl, C₁ to C₁₂ substituted heterocycloalkyl, cyclic C₂ to C₇ alkylene, substituted cyclic C₂ to C₇ alkylene, cyclic C₂ to C₇,

heteroalkylene, substituted cyclic C₂ to C₇,
heteroalkylene, hydroxymethyl or protected hydroxymethyl;
or

5 where R₆ and R₇ are directly attached to each other are,
they are, collectively, C₁ to C₅ alkylene, C₂ to C₅
alkenylene, C₂ to C₅ alkynylene, C₁ to C₅ substituted
alkylene, C₂ to C₅ substituted alkenylene, C₂ to C₅
substituted alkynylene, substituted epimino, C₁ to C₅
10 substituted alkylene epimino, thio, C₁ to C₅ alkylene
thio, C₁ to C₅ substituted alkylene thio, sulfonyl, C₁ to
C₅ alkylene sulfonyl, C₁ to C₅ substituted alkylene
sulfonyl, sulfinyl, C₁ to C₅ alkylene sulfinyl, C₁ to C₅
substituted alkylene sulfinyl, oxy, C₁ to C₅ alkylene oxy,
15 C₁ to C₅ substituted alkylene oxy, C₁ to C₅ alkylene dioxy,
C₁ to C₅ substituted alkylene dioxy, C₁ to C₅ alkylene
trioxy or C₁ to C₅ substituted alkylene trioxy; and

R₈ and, if present, R₉ are, independently, a hydrogen
20 atom, C₁ to C₁₂ alkyl, C₂ to C₁₂ alkenyl, C₂ to C₁₂ alkynyl,
C₁ to C₁₂ substituted alkyl, C₂ to C₁₂ substituted alkenyl,
C₂ to C₁₂ substituted alkynyl, C₃ to C₇ cycloalkyl, C₃ to
C₇ substituted cycloalkyl, C₅ to C₇ cycloalkenyl, C₅ to C₇
substituted cycloalkenyl, heterocyclic ring, substituted
25 heterocyclic ring, C₇ to C₁₈ phenylalkyl, C₇ to C₁₈
substituted phenylalkyl, C₁ to C₁₂ heterocycloalkyl, C₁ to
C₁₂ substituted heterocycloalkyl, phenyl, substituted
phenyl, naphthyl, substituted naphthyl, cyclic C₂ to C₇
alkylene, substituted cyclic C₂ to C₇ alkylene, cyclic C₂
30 to C₇ heteroalkylene, substituted cyclic C₂ to C₇
heteroalkylene, protected hydroxymethyl, protected amino,
(monosubstituted)amino, protected (monosubstituted)amino,
(disubstituted)amino, C₁ to C₁₀ alkylamino, C₁ to C₁₀ alkyl

protected amino, C₁ to C₁₀ alkyl (monosubstituted)amino, C₁ to C₁₀ alkyl, protected (monosubstituted)amino, C₁ to C₁₀ alkyl(disubstituted)amino, C₁ to C₁₀ substituted alkylamino, C₁ to C₁₀ substituted alkyl protected amino, C₁ to C₁₀ substituted alkyl (monosubstituted)amino, C₁ to C₁₀ substituted alkyl protected (monosubstituted)amino, C₁ to C₁₀ substituted alkyl(disubstituted)amino, carboxamide, 5 protected carboxamide or (i) the formula -C(O)NR¹¹R¹², (ii) the formula -C(O)R¹¹, (iii) the formula -NR¹¹R¹² or 10 (iv) the formula -C(O)OR¹¹, wherein R¹¹ and R¹² are, independently, a hydrogen atom, C₁ to C₁₂ alkyl, C₁ to C₁₂ substituted alkyl, C₂ to C₁₂ alkenyl, C₂ to C₁₂ substituted alkenyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C₇ to C₁₈ phenylalkyl, C₇ to C₁₈ 15 substituted phenylalkyl, C₁ to C₁₂ heterocycloalkyl, C₁ to C₁₂ substituted heterocycloalkyl, heteroaryl, substituted heteroaryl, heterocycle, substituted heterocycle, C₁ to C₁₂ acyl, C₁ to C₁₂ substituted acyl, phenylsulfonyl, substituted phenylsulfonyl, C₁ to C₁₀ alkylsulfonyl, C₁ to 20 C₁₀ substituted alkylsulfonyl, C₁ to C₁₂ alkylaminocarbonyl, C₁ to C₁₂ substituted alkylaminocarbonyl, phenylaminocarbonyl or substituted phenylaminocarbonyl; or

25 R₈ and R₉, together with the adjoining nitrogen depicted in structure B are, collectively, heterocycle or substituted heterocycle.

In one aspect of the above-described invention, 30 there is the proviso that, if X is carbonyl, R₈ is not alkoxy.

In another aspect of the above-described invention, there is the proviso that X can only be absent where R₆ and R₇ are not directly attached to each other.

5 The subject invention also provides a salt of the above-described compound.

In another embodiment, the subject invention provides a compound or combinatorial library where:

10

R₁ and R₄ are, independently, a hydrogen atom, halo, C₁ to C₁₂ alkyl or C₁ to C₁₂ substituted alkyl.

In an additional embodiment:

15

one of R₂ and R₃ is a hydrogen atom, halo, C₁ to C₁₂ alkyl and C₁ to C₁₂ substituted alkyl; and the other of R₂ and R₃ is selected from the group consisting of hydrogen atom, halo, hydroxy, carboxy, thio, carboxamide, the formula

20

-C(O)NR¹¹R¹² or the formula S(O)₂NR¹¹R¹², wherein R¹¹ and R¹² are, independently, a hydrogen atom, C₁ to C₁₂ alkyl, C₁ to C₁₂ substituted alkyl, C₂ to C₁₂ alkenyl, C₂ to C₁₂ substituted alkenyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C₇ to C₁₈ phenylalkyl, C₇ to C₁₈ substituted phenylalkyl, C₁ to C₁₂ heterocycloalkyl or C₁ to C₁₂ substituted heterocycloalkyl.

25

In a further embodiment:

30

R₆ and R₇ are not directly attached to each other and are, independently, a hydrogen atom, C₁ to C₁₂ alkyl, C₁ to C₁₂ substituted alkyl, C₃ to C₇ cycloalkyl or C₃ to C₇ substituted cycloalkyl.

In another embodiment:

R₈ and, if present, R₉ are, independently, a hydrogen atom, C₁ to C₁₂ alkyl, C₂ to C₁₂ alkenyl, C₂ to C₁₂ alkynyl, 5 C₁ to C₁₂ substituted alkyl, C₂ to C₁₂ substituted alkenyl, C₃ to C₇ cycloalkyl, C₃ to C₇ substituted cycloalkyl, C₅ to C₇ cycloalkenyl, C₅ to C₇ substituted cycloalkenyl, heterocyclic ring, substituted heterocyclic ring, C₇ to C₁₈ phenylalkyl, C₇ to C₁₈ substituted phenylalkyl, C₁ to 10 C₁₂ heterocycloalkyl, C₁ to C₁₂ substituted heterocycloalkyl, phenyl, substituted phenyl, cyclic C₂ to C₇ alkylene, substituted cyclic C₂ to C₇ alkylene, cyclic C₂ to C₇ heteroalkylene or substituted cyclic C₂ to C₇ heteroalkylene.

15

In a further embodiment, R₈ and R₉, together with the adjoining nitrogen depicted in structure B are, collectively, a heterocycle or substituted heterocycle.

20

Another embodiment of the present invention provides that R₅ is C₁ to C₈ alkylene or C₁ to C₈ substituted alkylene.

25

In another aspect of the present invention, R₆ and R₇ are directly attached to each other and are, collectively, a C₁ to C₅ alkylene or C₁ to C₅ substituted alkylene.

30

A further aspect of the invention is where X is absent. In addition, X can be carbonyl or sulfonyl.

In a further embodiment of the present invention:

R₁ and R₄, and one of R₂ and R₃, are, independently, a
5 hydrogen atom, halo, protected hydroxy, cyano, C₁ to C₁₂ alkyl, C₂ to C₁₂ alkenyl, C₂ to C₁₂ alkynyl, C₁ to C₁₂ substituted alkyl, C₂ to C₁₂ substituted alkenyl, C₂ to C₁₂ substituted alkynyl, C₁ to C₁₂ alkoxy, C₁ to C₁₂ substituted alkoxy, phenyl, substituted phenyl,
10 (disubstituted)amino, C₁ to C₁₀ alkylthio or C₁ to C₁₀ substituted alkylthio;

the other of R₂ and R₃ is a hydrogen atom, halo, hydroxy, carboxy, thio, carboxamide, the formula -C(O)NR¹¹R¹² or the
15 formula S(O)₂NR¹¹R¹², wherein R¹¹ and R¹² are, independently, a hydrogen atom, C₁ to C₁₂ alkyl, C₁ to C₁₂ substituted alkyl, C₂ to C₁₂ alkenyl, C₂ to C₁₂ substituted alkenyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C₇ to C₁₈ phenylalkyl, C₇ to C₁₈ substituted phenylalkyl,
20 C₁ to C₁₂ heterocycloalkyl or C₁ to C₁₂ substituted heterocycloalkyl; and

where R₆ and R₇ are not directly attached to each other, they are, independently, a hydrogen atom, C₁ to C₁₂ alkyl,
25 C₁ to C₁₂ substituted alkyl, C₃ to C₇ cycloalkyl or C₃ to C₇ substituted cycloalkyl;

R₈ and, if present, R₉ are, independently, a hydrogen atom, C₁ to C₁₂ alkyl, C₂ to C₁₂ alkenyl, C₂ to C₁₂ alkynyl,
30 C₁ to C₁₂ substituted alkyl, C₂ to C₁₂ substituted alkenyl, C₃ to C₇ cycloalkyl, C₃ to C₇ substituted cycloalkyl, C₅ to C₇ cycloalkenyl, C₅ to C₇ substituted cycloalkenyl, heterocyclic ring, substituted heterocyclic ring, C₇ to

C₁₈ phenylalkyl, C₇ to C₁₈ substituted phenylalkyl, C₁ to C₁₂ heterocycloalkyl, C₁ to C₁₂ substituted heterocycloalkyl, phenyl, substituted phenyl, cyclic C₂ to C₇ alkylene, substituted cyclic C₂ to C₇ alkylene, cyclic

5 C₂ to C₇ heteroalkylene or substituted cyclic C₂ to C₇ heteroalkylene; or

R₈ and R₉, together with the adjoining nitrogen depicted in structure B are, collectively, a heterocycle or

10 substituted heterocycle; and

R₅ is C₁ to C₈ alkylene or C₁ to C₈ substituted alkylene; and

15 where R₆ and R₇ are directly attached to each other, they are, collectively, C₁ to C₅ alkylene or C₁ to C₅ substituted alkylene; and

20 X is absent or present and, if present, is carbonyl or sulfonyl.

In an additional embodiment of the present invention, Z is the structure A. Further, provided is where the cyclic portion of structure A is 1,4-piperazine

25 or 1,4-homopiperazine. In another embodiment, Z is the structure B.

In a further embodiment, R₆ and R₇ are directly attached to each other. Additionally is provided where R₆

30 and R₇ are not directly attached to each other.

In another embodiment:

R₁ and R₄ are each hydrogen; and

5 one of R₂ and R₃ is hydrogen and the other is the formula -C(O)NR¹¹R¹², wherein one of R¹¹ and R¹² is hydrogen and the other is 2-morpholin-4-yl-ethyl, 3-pyrrolidin-1-yl-propyl, allyl, 3-fluorobenzyl, 2-piperidin-1-yl-ethyl, 4-morpholino-3-propyl, ethyl-4-butyryl, 2-methoxyethyl, 10 benzyl, 4-methylbenzyl, N,N-diethylethylene, N,N-diethyl-1,3-propylene, 3,5-dimethoxybenzyl, 4-fluorophenethyl, 4-fluorobenzyl, 2-fluorophenethyl, 2-(3,4-dimethoxyphenyl)ethyl, 2-pyridin-2-yl-ethyl, propargyl, 2-pyrrolidin-1-yl-ethyl, 2-chlorobenzyl, cyclopropyl, 15 pyridin-3-yl-methyl, 2-thiophenemethyl, 3-(methylthio)propyl, cyclohexanemethyl, 2-ethoxyethyl, cyclopentyl, cyclohexyl, 3-chlorobenzyl, 4-methoxyphenethyl, 2-(4-chlorophenyl)ethyl, 3-dimethylamino-1-propyl, 3,4-dimethoxybenzyl, 2-20 bromobenzyl, N-(3-propyl)-N-methylaniline, 2-propionic acid, 2-(3-phenyl)-propionic acid, 2-(4-methyl)-pentanoic acid, (±)-tetrahydrofuryl, 3-imidazol-1-yl-propyl, 2-trifluoromethylbenzyl, cycloheptyl, 2,4-dichlorophenethyl, 1-(3-propyl)-25 pyrrolidin-2-one, 4-tert-butylcyclohexyl, 2,2,6,6-tetramethyl-piperidin-4-yl, 5-diethylamino-2-pentyl, 1,3-dimethylbutyl, 2,4-dimethylbenzyl, thiophene-2-ethyl, 4-methoxyphenyl, 4-piperidino-1-carboxylic acid ethyl ester, 3-methoxybenzyl, N-1-ethyl-N-1-m-tolyl-2-ethyl, 1-30 benzyl-piperidin-4-yl, 1-methyl-3-phenylpropyl, 2-fluorobenzyl, 3-(trifluoromethyl)benzyl, piperonyl, 1-naphthalenemethyl, 3,4-dichlorobenzyl, (R)-(-)-1-cyclohexylethyl, (+/-)-1-(1-naphthyl)ethyl,

4-(trifluoromethoxy)benzyl or 5-guanidinopentanoic acid-2-yl.

In a further embodiment:

5

Z is the structure A or the structure C, where:

X is carbonyl and the combination of X-R₈ is benzoyl, methoxyacetyl, tert-buty lacetyl, 2,4-difluorobenzoyl, 10 2,4-dimethylbenzoyl, 2-ethylhexanoyl, 2-propylpentanoyl, 3-indolepropionyl, N-phenylanthranilyl, trans-2-carboxycyclohexanoyl, cyclohex-3-en-oyl, trans-pent-2-en-oyl, 1-methyl-1-cyclohexanoyl, 1-acetyl piperidine-4-carbonyl, cyclopropanecarbonyl, methanesulfonyl acetyl, 15 5-hexynoyl, 3-furoyl, 3,4-difluorophenyl acetyl, 3-benzoyl-benzoyl, 2-(trifluoromethyl)phenyl acetyl, 4-(trifluoromethyl)phenyl acetyl, 2-acetyl amino-3-(1H-indol-3-yl)-propionyl, 3-(phenylsulfonyl)propionyl, 2-benzyl oxyphenyl acetyl, benzo(b)thiophene-3-acetyl, 20 3-fluoro-2-methyl-benzoyl, 1-methylcyclopropane-1-carboxyl, (-)-menthoxyacetyl, cyclohexyl-1-acetic acid-1-methyl carbonyl, 2-(3-trifluoromethyl-phenyl amino)-benzoyl, 2-ketobutyryl, 2-ethyl-2-hydroxybutyryl, 5-chlorovaleryl, 1-acetyl-pyrrolidine-2-carbonyl, 5-chlorothiophene-2-carboxylyl, 2-(2-methoxyethoxy)acetyl, 25 2-methyl-3-furoyl, 6-heptynoyl or 5-methylisoxazole-4-carbonyl; or

X is sulfonyl and the combination of X-R₈ is 2-mesitylenesulfonyl, 2-naphthenesulfonyl, 2-thiophenesulfonyl, 4-chlorobenzenesulfonyl, 4-fluorobenzenesulfonyl, N-acetyl sulfanilyl, 2-acetomide-4-methyl-5-thiazolesulfonyl, 4-tert-butylbenzenesulfonyl,

8-quinolinesulfonyl, 3-chloro-4-fluorobenzenesulphonyl,
4-ethylbenzenesulfonyl, pentamethylbenzenesulfonyl, 2,4-
dichlorobenzenesulphonyl, 2-chloro-6-
methylbenzenesulphonyl, 3,4-difluorobenzenesulphonyl,
5 3,5-dichlorobenzenesulfonyl, 3-chlorobenzenesulfonyl, 3-
fluorobenzenesulphonyl, 4-
trifluoromethylbenzenesulphonyl,
2-(methoxycarbonyl)thiophene-3-sulfonyl, 1-
methylimidazole-4-sulfonyl, 3-chloro-4-
10 methylbenzenesulfonyl, 4-isopropylbenzenesulphonyl, 3,4-
dichlorobenzenesulfonyl, 1-naphthalenesulfonyl, 3-
nitrobenzenesulfonyl, 4-bromobenzenesulfonyl, 4-
nitrobenzenesulfonyl, 2,3,5,6-tetramethylbenzenesulfonyl,
p-xylene-2-sulfonyl, 4-n-propylbenzenesulfonyl, 4-n-
15 amylbenzenesulfonyl, 2-chlorobenzenesulfonyl, 5-
chlorothiophene-2-sulfonyl, m-toluenesulfonyl, 2-
bromobenzenesulfonyl, p-styrenesulfonyl, 4-pentylbenzene-
1-sulfonyl, 4-n-butylbenzenesulfonyl or 2-
methylsulfonylbenzenesulfonyl.

20

Another embodiment of the present invention
provides a single compound or combinatorial library
where:

25 Z is the structure A, where:

m is 0;

R₅ is 1,4-butylene, 1,2-ethylene or 1,3-propylene;

30

R₆ and R₇ are directly attached and, combined, is 1,2-
ethylene; or R₆ and R₇ are not directly attached and are

20

each selected from the group consisting of hydrogen and ethyl.

In an additional embodiment:

5

Z is structure A, wherein:

m is 1;

10 n is 3;

R₅ is 1,2-ethylene; and

15 R₆ and R₇ are directly attached and, combined, is 1,2-ethylene.

In yet another embodiment:

Z is structure C, wherein:

20

K is absent or, if present, is 1,3-propylene.

25 The present invention also provides where Z is structure B. In a further embodiment, the cyclic portion of structure B is pyrrolidine, piperidine or piperazine.

In another embodiment:

30 the cyclic portion of structure B is 1,2-pyrrolidene, 1,2-piperidene or 1,4-piperazene, where R₅ is directly connected at the 2-position, 2-position and 4-position, respectively, of the cyclic portion; and

R₅ is methylene or ethylene; and

R₈ and R₉ are, independently, hydrogen, methyl, ethyl, hydroxyethyl, benzyl, cyclohexyl, isobutyl, propyl, 5 butyl, sec-butyl, hexyl, heptyl, allyl, cyanoethyl, 2-picollyl, cyclohexylmethyl, cyclohexylethane-1,1-diyl, N,N-diethylaminoethyl, N,N-dimethylaminopropyl or neopentyl; or

10 R₈ and R₉, together with the adjoining nitrogen atom depicted in structure B are, collectively, pyrrolidin-1-yl, piperidin-1-yl, 3-(carboxamide)piperidin-1-yl, 2-(carboxamide)pyrrolidin-1-yl, 4-(methyl)piperazin-1-yl, morpholin-4-yl, 2-(hydroxymethyl)piperidin-1-yl, 4-15 (ethylcarboxylate)piperidin-1-yl, 4-(phenyl)piperazin-1-yl, 4-(2-pyrimidyl)-piperazin-1-yl, thiomorpholin-4-yl, 4-(benzyl)piperazin-1-yl, 3-(ethylcarboxylate)piperidin-1-yl, 4-(hydroxy)piperidin-1-yl, 3,5-(dimethyl)piperazin-1-yl, homopiperazin-1-yl, 4-(methyl)homopiperazin-1-yl, 20 2-(methyl)piperidin-1-yl, 3,5-(dimethyl)piperidin-1-yl, 3-(N,N-dimethylamino)pyrrolidin-1-yl, 3-(amino)pyrrolidin-1-yl, homopiperidin-1-yl, decahydroquinolin-1-yl or tetrahydroisoquinolin-1-yl.

25 The invention also provides methods of preparing 2-aminobenzoxazole derivative compounds and combinatorial libraries. In one method, such compounds and libraries can be prepared by starting with, for example, an aldehyde (SASRIN) resin, which can be reacted 30 with a primary amine to form a disubstituted amine attached to resin. See Step 1 of Figure 1 and Step 1 of Figure 3.

Alternatively, other resins, such as an mBHA Linker resin, can be used. See Figure 2.

Resin-bound 2-aminobenzoxazole derivative
5 compounds can be cleaved by treating them, for example, with a solution of trifluoroacetic acid in dichloromethane (TFA/DCM). With derivatives attached to mBHA Linker resin, cleavage can be achieved using hydrofluoric acid (HF) gas. The compounds can be
10 extracted from the spent resin, for example, with acetic acid (AcOH).

A resin-attached amine can be acylated with a benzoxazole derivative that is carboxy-substituted on the
15 benzyl portion of the bicyclic ring. The carboxy substitution can be, for example, at the 5- or 6-position. See Step 2 of Figure 2 and Step 2 of Figure 3. However, it should be understood that the substitution can occur, for example, at the 4- or 7-position.

20 It should also be understood that the benzyl portion of the benzoxazole may be substituted by a variety of other moieties, such as a sulfonyl, which would result in a sulfonamide at that position of the
25 final product. Alternatively, a resin-bound hydroxy can react with the carboxy group of the benzoxazole, resulting in a carboxy moiety at that position of the final product. In addition, a resin-bound halide can react with a phenol (OH) group attached to the 4- to 7-
30 position (i.e., R₁ to R₄) of the benzoxazole ring, resulting in a hydroxy group at that position of the final product. Similarly, a resin-bound halide can react with an -SH group attached to the 4- to 7-position (i.e.,

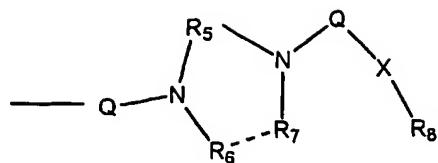
R_1 to R_4) of the benzoxazole ring, resulting in an -SH group at that position of the final product.

Moreover, a resin-bound halide can react with 5 an -OH group attached to the 4- to 7-position (i.e., R_1 to R_4) of the benzoxazole ring, resulting in an -OH group at that position of the final product. The resin can then be cleaved. The resulting product can then react with an alkyl halide or substituted alkyl halide in solution, 10 resulting in an -OR at that position.

It should also be understood that the benzoxazole derivative introduced in this step may be further substituted at any or all of the other positions 15 of the benzene ring (R_1 to R_4 of the claimed invention). For example, a variety of substituted 1,2-aminophenols are commercially available in the Available Chemicals Directory, many with functional groups capable of attachment to resin. In such cases, the benzoxazole ring 20 could be formed first in solution.

The benzoxazole derivative can be further substituted with a leaving group, such as methylthio, at, for example, the 2-position or other positions on the 25 benzyl ring. Other possible leaving groups include chloro and bromo.

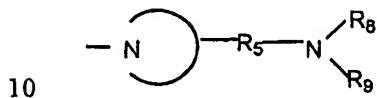
The leaving group can be displaced with a diamine derivative or an amino alcohol derivative. Such 30 a moiety can be, for example, formula A:



(excluding "-X-R₈" of formula A);

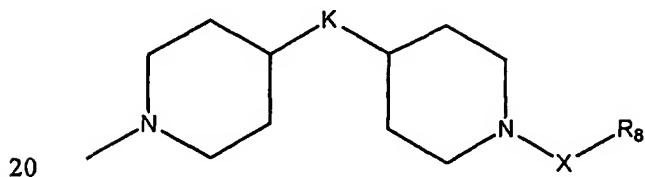
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or formula B:



(excluding "-NR₈R₉" of formula B and first having a
15 hydroxy attached to R₅ (i.e., -R₅-OH));

or formula C:



(excluding "-X-R₈" of formula C). See Step 3 of Figure 1,
where Formula A (where Q is absent) is attached; and
25 Step 3 of Figure 3, where Formula B (where R₅ is
methylene) is attached.

As discussed above, in formula A, Q is the
formula $((\text{CH}_2)_n\text{NH})_m$, where m is 0 or 1, n is 1 to 6 and
30 the alkylene portion of Q is directly attached to the
depicted nitrogen atom in formula A; and the dotted line

between R_6 and R_7 , which are variable groups, indicates that R_6 and R_7 are optionally directly attached.

5 In formula B, the depicted cyclic portion is an unsubstituted or substituted heterocycle that is fully saturated, contains 4 to 7 ring atoms, 1 to 2 nitrogen rings atoms and 0 to 1 other heteroatoms selected from oxygen and sulfur, and R_5 , R_8 and R_9 are variable groups.

10 In formula C, K is absent or present and, if present, is a C_1 to C_{12} alkylene, X is optionally present as a carbonyl, thiocarbonyl, thioester, sulfonyl or sulfinyl group, and R_8 is a variable group.

15 Preferentially, diamines are symmetrical to avoid generation of regioisomeric mixtures. However, assymetrical diamines may be used, for example, 1,2-diaminopropane, lysine or 2,3-diaminopropionic acid. Diamines can have either primary or secondary amine
20 termini.

The present invention further provides attachment of $-Q-X-R_8$ of formula A or $-X-R_8$ of formula C to the rest of the formula by, for example acylation.
25 Alternatively, attachment of $-Q-X-R_8$ of formula A or $-X-R_8$ of formula C to the rest of the formula can be accomplished by sulfonation. See Step 4 of Figure 1. It should also be understood that this attachment can be done via other mechanisms, such as sulfination and
30 thioacetylation.

The method of the present invention also provides where the disubstituted amino ($-NR_8R_9$) portion of

formula B is attached to the rest of the formula by displacing a leaving group. Such a leaving group can be, for example, a halo and, more specifically, bromo. See Steps 4 and 5 of Figure 3.

5

When the above-described compounds include one or more chiral centers, the stereochemistry of such chiral centers can independently be in the R or S configuration, or a mixture of the two. The chiral 10 centers can be further designated as R or S or R,S or d,D, l,L or d,l, D,L.

Regarding the compounds and combinatorial libraries described herein, the suffix "ene" added to any 15 of the described terms means that two parts of the substituent are each connected to two other parts in the compound (unless the substituent contains only one carbon, in which case such carbon is connected to two other parts in the compound, for example, methylene).

20

The term "C₁ to C₁₂ alkyl" denotes such radicals as methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, amyl, tert-amyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl and the 25 like. Preferred "C₁ to C₁₂ alkyl" groups are methyl, ethyl, iso-butyl, sec-butyl and iso-propyl. Similarly, the term "C₁ to C₁₂ alkylene" denotes radicals of 1 to 12 carbons connected to two other parts in the compound.

30

The term "C₂ to C₁₂ alkenyl" denotes such radicals as vinyl, allyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl,

5-heptenyl, 6-heptenyl, (as well as octenyl, nonenyl, decenyl, undecenyl, dodecenyl radicals attached at any appropriate carbon position and the like) as well as dienes and trienes of straight and branched chains.

5

The term "C₂ to C₁₂ alkynyl" denotes such radicals as ethanol, propynyl, 2-butynyl, 2-pentynyl, 3-pentynyl, 2- hexynyl, 3-hexynyl, 4-hexynyl, 2-heptynyl, 3-heptynyl, 4- heptynyl, 5-heptynyl (as well as octynyl, 10 nonynyl, decynyl, undecynyl, dodecynyl radicals attached at any appropriate carbon position and the like) as well as di- and tri-ynes of straight and branched chains.

The terms "C₁ to C₁₂ substituted alkyl," "C₂ to C₁₂ substituted alkenyl," "C₂ to C₁₂ substituted alkynyl," "C₁ to C₁₂ substituted alkylene," "C₂ to C₁₂ substituted alkenylene" and "C₂ to C₁₂ substituted alkynylene" denote groups are substituted by one or more, and preferably one or two, halogen, hydroxy, protected hydroxy, oxo, 15 protected oxo, C₃ to C₇ cycloalkyl, phenyl, naphthyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, guanidino, protected guanidino, heterocyclic ring, substituted 20 heterocyclic ring, imidazolyl, indolyl, pyrrolidinyl, C₁ to C₁₂ alkoxy, C₁ to C₁₂ acyl, C₁ to C₁₂ acyloxy, nitro, carboxy, protected carboxy, carbamoyl, carboxamide, 25 protected carboxamide, N-(C₁ to C₁₂ alkyl)carboxamide, protected N-(C₁ to C₁₂ alkyl)carboxamide, N,N-di(C₁ to C₁₂ alkyl)carboxamide, cyano, methylsulfonylamino, thiol, C₁ 30 to C₁₀ alkylthio or C₁ to C₁₀ alkylsulfonyl groups. The substituted alkyl groups may be substituted once or more, and preferably once or twice, with the same or with different substituents.

Examples of the above substituted alkyl groups include the 2-oxo-prop-1-yl, 3-oxo-but-1-yl, cyanomethyl, nitromethyl, chloromethyl, hydroxymethyl,
5 tetrahydropyranyloxymethyl, trityloxymethyl, propionyloxymethyl, aminomethyl, carboxymethyl, allyloxycarbonylmethyl, allyloxycarbonylaminomethyl, methoxymethyl, ethoxymethyl, t-butoxymethyl, acetoxymethyl, chloromethyl, bromomethyl, iodomethyl,
10 trifluoromethyl, 6-hydroxyhexyl, 2,4-dichloro(n-butyl), 2-aminopropyl, 1-chloroethyl, 2-chloroethyl, 1-bromoethyl, 2-chloroethyl, 1-fluoroethyl, 2-fluoroethyl, 1-iodoethyl, 2-iodoethyl, 1-chloropropyl, 2-chloropropyl, 3-chloropropyl, 1-bromopropyl, 2-bromopropyl, 3-bromopropyl, 1-fluoropropyl, 2-fluoropropyl, 3-fluoropropyl, 1-iodopropyl, 2-iodopropyl, 3-iodopropyl, 2-aminoethyl, 1-aminoethyl, N-benzoyl-2-aminoethyl, N-acetyl-2-aminoethyl, N-benzoyl-1-aminoethyl, N-acetyl-1-aminoethyl and the like.

20

Examples of the above substituted alkenyl groups include styrenyl, 3-chloro-propen-1-yl, 3-chloro-buten-1-yl, 3-methoxy-propen-2-yl, 3-phenyl-buten-2-yl, 1-cyano-buten-3-yl and the like. The geometrical isomerism is not critical, and all geometrical isomers for a given substituted alkenyl can be used.

30 Examples of the above substituted alkynyl groups include phenylacetylen-1-yl, 1-phenyl-2-propyn-1-yl and the like.

The term "oxo" denotes a carbon atom bonded to two additional carbon atoms substituted with an oxygen

atom doubly bonded to the carbon atom, thereby forming a ketone moiety.

The term "protected oxo" denotes a carbon atom
5 bonded to two additional carbon atoms substituted with
two alkoxy groups or twice bonded to a substituted diol
moiety, thereby forming an acyclic or cyclic ketal
moiety.

10 The term "C₁ to C₁₂ alkoxy" as used herein
denotes groups such as methoxy, ethoxy, n-propoxy,
isopropoxy, n-butoxy, t-butoxy and like groups. A
preferred alkoxy is methoxy. The term "C₁ to C₁₂
substituted alkoxy" means the alkyl portion of the alkoxy
15 can be substituted in the same manner as in relation to C₁
to C₁₂ substituted alkyl. Similarly, the term "C₁ to C₁₂
phenylalkoxy" as used herein means "C₁ to C₁₂ alkoxy"
bonded to a phenyl radical.

20 The term "C₁ to C₁₂ acyloxy" denotes herein
groups such as formyloxy, acetoxy, propionyloxy,
butyryloxy, pivaloyloxy, pentanoyloxy, hexanoyloxy,
heptanoyloxy, octanoyloxy, nonanoyloxy, decanoyloxy,
undecanoyloxy, dodecanoyloxy and the like.

25 Similarly, the term "C₁ to C₁₂ acyl" encompasses
groups such as formyl, acetyl, propionyl, butyryl,
pentanoyl, pivaloyl, hexanoyl, heptanoyl, octanoyl,
nonanoyl, decanoyl, undecanoyl, dodecanoyl, benzoyl and
30 the like. Preferred acyl groups are acetyl and benzoyl.

The term "C₁ to C₁₂ substituted acyl" denotes
the acyl group substituted by one or more, and preferably

one or two, halogen, hydroxy, protected hydroxy, oxo, protected oxo, cyclohexyl, naphthyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, guanidino, 5 heterocyclic ring, substituted heterocyclic ring, imidazolyl, indolyl, pyrrolidinyl, C₁ to C₁₂ alkoxy, C₁ to C₁₂ acyl, -C₁ to C₁₂ acyloxy, nitro, C₁ to C₁₂ alkyl ester, carboxy, protected carboxy, carbamoyl, carboxamide, protected carboxamide, N-(C₁ to C₁₂ alkyl)carboxamide, 10 protected N-(C₁ to C₁₂ alkyl)carboxamide, N,N-di(C₁ to C₁₂ alkyl)carboxamide, cyano, methylsulfonylamino, thiol, C₁ to C₁₀ alkylthio or C₁ to C₁₀ alkylsulfonyl groups. The substituted acyl groups may be substituted once or more, and preferably once or twice, with the same or with 15 different substituents.

Examples of C₁ to C₁₂ substituted acyl groups include 4-phenylbutyroyl, 3-phenylbutyroyl, 3-phenylpropanoyl, 2- cyclohexanylacetyl, 20 cyclohexanecarbonyl, 2-furanoyl and 3-dimethylaminobenzoyl.

The substituent term "C₃ to C₇ cycloalkyl" includes the cyclopropyl, cyclobutyl, cyclopentyl, 25 cyclohexyl or cycloheptyl rings. Similarly, a substituent that can be C₃ to C₇ cycloalkyl" can also be "C₅ to C₇ cycloalkyl," which includes the cyclopentyl, cyclohexyl or cycloheptyl rings.

30 The substituent term "C₃ to C₇ substituted cycloalkyl" or "C₅ to C₇ substituted cycloalkyl" indicates the above cycloalkyl rings substituted by one or two halogen, hydroxy, protected hydroxy, C₁ to C₁₀ alkylthio,

C_1 to C_{10} alkylsulfoxide, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylthio, C_1 to C_{10} substituted alkylsulfoxide, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkyl, C_1 to C_{12} alkoxy, oxo, protected oxo, (monosubstituted)amino, (disubstituted)amino, trifluoromethyl, carboxy, protected carboxy, phenyl, substituted phenyl, phenylthio, phenylsulfoxide, phenylsulfonyl, amino, or protected amino groups.

10

The term "cycloalkylene" means a cycloalkyl, as defined above, where the cycloalkyl radical is bonded at two positions connecting together two separate additional groups. Similarly, the term "substituted cycloalkylene" means a cycloalkylene where the cycloalkyl radical is bonded at two positions connecting together two separate additional groups and further bearing at least one additional substituent.

20

The term " C_5 to C_7 cycloalkenyl" indicates a 1,2, or 3-cyclopentenyl ring, a 1,2,3 or 4-cyclohexenyl ring or a 1,2,3,4 or 5-cycloheptenyl ring, while the term "substituted C_5 to C_7 cycloalkenyl" denotes the above C_5 to C_7 cycloalkenyl rings substituted by a C_1 to C_{12} alkyl radical, halogen, hydroxy, protected hydroxy, C_1 to C_{12} alkoxy, trifluoromethyl, carboxy, protected carboxy, oxo, protected oxo, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, phenyl, substituted phenyl, amino, or protected amino.

25

The term " C_5 to C_7 cycloalkenylene" is a cycloalkenyl ring, as defined above, where the cycloalkenyl radical is bonded at two positions

connecting together two separate additional groups.

Examples of C₅ to C₇ cycloalkenylenes include

1,3-cyclopentylene and 1,2-cyclohexylene.

5 Similarly, the term "substituted C₅ to C₇ cycloalkenylene" means a cycloalkenylene further substituted by halogen, hydroxy, protected hydroxy, C₁ to C₁₀ alkylthio, C₁ to C₁₀ alkylsulfoxide, C₁ to C₁₀ alkylsulfonyl, C₁ to C₁₀ substituted alkylthio, C₁ to C₁₀ 10 substituted alkylsulfoxide, C₁ to C₁₀ substituted alkylsulfonyl, C₁ to C₁₂ alkyl, C₁ to C₁₂ alkoxy, C₁ to C₁₂ substituted alkyl, C₁ to C₁₂ alkoxy, oxo, protected oxo, (monosubstituted)amino, (disubstituted)amino, trifluoromethyl, carboxy, protected carboxy, phenyl, 15 substituted phenyl, phenylthio, phenylsulfoxide, phenylsulfonyl, amino, or protected amino group.

Examples of substituted C₅ to C₇ cycloalkenylenes include 4-chloro-1,3-cyclopentylene and 4-methyl-1,2-cyclohexylene.

20 The term "heterocycle" or "heterocyclic ring" denotes optionally substituted five-membered to eight-membered rings that have 1 to 4 heteroatoms, such as oxygen, sulfur and/or nitrogen, in particular nitrogen, either alone or in conjunction with sulfur or oxygen ring 25 atoms. These five-membered to eight-membered rings may be saturated, fully unsaturated or partially unsaturated, with fully saturated rings being preferred. Preferred heterocyclic rings include morpholino, piperidinyl, piperazinyl, 2-amino-imidazoyl, tetrahydrofuran-yl, 30 pyrrolo, tetrahydrothiophen-yl, hexylmethleneimino and heptylmethyleneimino.

The term "substituted heterocycle" or "substituted heterocyclic ring" means the above-described heterocyclic ring is substituted with, for example, one or more, and preferably one or two, substituents which

5 are the same or different which substituents can be halogen, hydroxy, protected hydroxy, cyano, nitro, C₁ to C₁₂ alkyl, -C₁ to C₁₂ alkoxy, C₁ to C₁₂ substituted alkoxy, C₁ to C₁₂ acyl, C₁ to C₁₂ acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl,

10 hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino carboxamide, protected carboxamide, N-(C₁ to C₁₂ alkyl)carboxamide, protected N-(C₁ to C₁₂ alkyl)carboxamide, N, N-di(C₁ to C₁₂

15 alkyl)carboxamide, trifluoromethyl, N-((C₁ to C₁₂ alkyl)sulfonyl)amino, N-(phenylsulfonyl)amino, heterocycle or substituted heterocycle groups.

The term "heteroaryl" means a heterocyclic aromatic derivative which is a five-membered or six-membered ring system having from 1 to 4 heteroatoms, such as oxygen, sulfur and/or nitrogen, in particular nitrogen, either alone or in conjunction with sulfur or oxygen ring atoms. Examples of heteroaryls include

25 pyridinyl, pyrimidinyl, and pyrazinyl, pyridazinyl, pyrrolo, furano, oxazolo, isoxazolo, phthalimido, thiazolo and the like.

The term "substituted heteroaryl" means the

30 above-described heteroaryl is substituted with, for example, one or more, and preferably one or two, substituents which are the same or different which substituents can be halogen, hydroxy, protected hydroxy,

cyano, nitro, C₁ to C₁₂ alkyl, C₁ to C₁₂ alkoxy, C₁ to C₁₂ substituted alkoxy, C₁ to C₁₂ acyl, C₁ to C₁₂ substituted acyl, C₁ to C₁₂ acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl,
5 protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C₁ to C₁₂ alkyl)carboxamide, protected N-(C₁ to C₁₂ alkyl)carboxamide, N, N-di(C₁ to C₁₂ alkyl)carboxamide,
10 trifluoromethyl, N-(C₁ to C₁₂ alkyl)sulfonyl)amino or N-(phenylsulfonyl)amino groups.

The term "C₇ to C₁₈ phenylalkyl" denotes a C₁ to C₁₂ alkyl group substituted at any position within the
15 alkyl chain by a phenyl. The definition includes groups of the formula: -phenyl-alkyl, -alkyl-phenyl and -alkyl-phenyl-alkyl. Examples of such a group include benzyl, 2-phenylethyl, 3-phenyl(n-propyl), 4-phenylhexyl, 3-phenyl(n-amyl), 3-phenyl(sec-butyl) and the like.
20 Preferred C₇ to C₁₈ phenylalkyl groups are any one of the preferred alkyl groups described herein combined with a phenyl group.

Similarly, the term "C₁ to C₁₂ heterocycloalkyl"
25 denotes a C₁ to C₁₂ alkyl group substituted at any position within the alkyl chain by a "heterocycle," as defined herein. The definition includes groups of the formula: -heterocyclic-alkyl, -alkyl-heterocyclic and -alkyl-heterocyclic-alkyl. Examples of such a group
30 include 2-pyridylethyl, 3-piperidyl(n-propyl), 4-furylhexyl, 3-piperazyl(n-amyl), 3-morpholyl(sec-butyl) and the like. Preferred C₁ to C₁₂ heterocycloalkyl groups are any one of the preferred alkyl groups described

herein combined with any one of the preferred heterocycle groups described herein.

The terms "C₇ to C₁₈ substituted phenylalkyl" and "C₁ to C₁₂ substituted heterocycloalkyl" denote a C₇ to C₁₈ phenylalkyl group or C₁ to C₁₂ heterocycloalkyl substituted (on the alkyl or, where applicable, phenyl or heterocyclic portion) with one or more, and preferably one or two, groups chosen from halogen, hydroxy, 10 protected hydroxy, oxo, protected oxo, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, guanidino, protected guanidino, heterocyclic ring, substituted heterocyclic ring, C₁ to C₁₂ alkyl, C₁ to C₁₂ substituted 15 alkyl, C₁ to C₁₂ alkoxy, C₁ to C₁₂ substituted alkoxy, C₁ to C₁₂ acyl, C₁ to C₁₂ substituted acyl, C₁ to C₁₂ acyloxy, nitro, carboxy, protected carboxy, carbamoyl, carboxamide, protected carboxamide, N-(C₁ to C₁₂ alkyl)carboxamide, protected N-(C₁ to C₁₂ 20 alkyl)carboxamide, N, N-(C₁ to C₁₂ dialkyl)carboxamide, cyano, N-(C₁ to C₁₂ alkylsulfonyl)amino, thiol, C₁ to C₁₀ alkylthio, C₁ to C₁₀ alkylsulfonyl groups; and/or the phenyl group may be substituted with one or more, and preferably one or two, substituents chosen from halogen, 25 hydroxy, protected hydroxy, cyano, nitro, C₁ to C₁₂ alkyl, C₁ to C₁₂ substituted alkyl, C₁ to C₁₂ alkoxy, C₁ to C₁₂ substituted alkoxy, C₁ to C₁₂ acyl, C₁ to C₁₂ substituted acyl, C₁ to C₁₂ acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, 30 protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C₁ to C₁₂ alkyl)carboxamide, protected N-(C₁ to C₁₂

alkyl)carboxamide, N, N-di(C₁ to C₁₂ alkyl)carboxamide, trifluoromethyl, N-((C₁ to C₁₂ alkyl)sulfonyl)amino, N-(phenylsulfonyl)amino, cyclic C₂ to C₁₂ alkylene or a phenyl group, substituted or unsubstituted, for a 5 resulting biphenyl group. The substituted alkyl, phenyl or heterocyclic groups may be substituted with one or more, and preferably one or two, substituents which can be the same or different.

10 Examples of the term "C₇ to C₁₈ substituted phenylalkyl" include groups such as 2-phenyl-1-chloroethyl, 2-(4-methoxyphenyl)ethyl, 4-(2,6-dihydroxy phenyl)n-hexyl, 2-(5-cyano-3-methoxyphenyl)n-pentyl, 3-(2,6-dimethylphenyl)n-propyl, 4-chloro-3-aminobenzyl, 6-15 (4-methoxyphenyl)-3-carboxy(n-hexyl), 5-(4-aminomethylphenyl)-3-(aminomethyl)n-pentyl, 5-phenyl-3-oxo-n-pent-1-yl and the like.

The term "C₇ to C₁₈ phenylalkylene" specifies a 20 C₇ to C₁₈ phenylalkyl, as defined above, where the phenylalkyl radical is bonded at two different positions connecting together two separate additional groups. The definition includes groups of the formula: -phenyl-alkyl-, -alkyl-phenyl- and -alkyl-phenyl-alkyl-. 25 Substitutions on the phenyl ring can be 1,2, 1,3 or 1,4. C₇ to C₁₈ phenylalkylenes include, for example, 1,4-tolylene and 1,3-xylylene.

Similarly, the term "C₁ to C₁₂ 30 heterocycloalkylene" specifies a C₁ to C₁₂ heterocycloalkyl, as defined above, where the heterocycloalkyl radical is bonded at two different positions connecting together two separate additional

groups. The definition includes groups of the formula:
-heterocyclic-alkyl-, -alkyl-heterocyclic and -alkyl-
heterocyclic-alkyl-.

5 The terms "C₁ to C₁₈ substituted phenylalkylene"
and "C₁ to C₁₂ substituted heterocycloalkylene" means a C₁
to C₁₈ phenylalkylene or C₁ to C₁₂ heterocycloalkylene as
defined above that is further substituted by halogen,
hydroxy, protected hydroxy, C₁ to C₁₀ alkylthio, C₁ to C₁₀
10 alkylsulfoxide, C₁ to C₁₀ alkylsulfonyl, C₁ to C₁₀
substituted alkylthio, C₁ to C₁₀ substituted
alkylsulfoxide, C₁ to C₁₀ substituted alkylsulfonyl, C₁ to
C₁₂ alkyl, C₁ to C₁₂ alkoxy, C₁ to C₁₂ substituted alkyl, C₁
to C₁₂ alkoxy, oxo, protected oxo, (monosubstituted)amino,
15 (disubstituted)amino, trifluoromethyl, carboxy, protected
carboxy, phenyl, substituted phenyl, phenylthio,
phenylsulfoxide, phenylsulfonyl, amino, or protected
amino group on the phenyl ring or on the alkyl group.

20 The term "substituted phenyl" specifies a
phenyl group substituted with one or more, and preferably
one or two, moieties chosen from the groups consisting of
halogen, hydroxy, protected hydroxy, cyano, nitro, C₁ to
C₁₂ alkyl, C₁ to C₁₂ substituted alkyl, C₁ to C₁₂ alkoxy, C₁
25 to C₁₂ substituted alkoxy, C₁ to C₁₂ acyl, C₁ to C₁₂
substituted acyl, C₁ to C₁₂ acyloxy, carboxy, protected
carboxy, carboxymethyl, protected carboxymethyl,
hydroxymethyl, protected hydroxymethyl, amino, protected
amino, (monosubstituted)amino, protected
30 (monosubstituted)amino, (disubstituted)amino,
carboxamide, protected carboxamide, N-(C₁ to C₁₂
alkyl)carboxamide, protected N-(C₁ to C₁₂
alkyl)carboxamide, N, N-di(C₁ to C₁₂ alkyl)carboxamide,

trifluoromethyl, N-((C₁ to C₁₂ alkyl)sulfonyl)amino, N-(phenylsulfonyl)amino or phenyl, wherein the phenyl is substituted or unsubstituted, such that, for example, a biphenyl results.

5

Examples of the term "substituted phenyl" includes a mono- or di(halo)phenyl group such as 2, 3 or 4-chlorophenyl, 2,6-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 2, 3 or 4-bromophenyl, 10 3,4-dibromophenyl, 3-chloro-4-fluorophenyl, 2, 3 or 4-fluorophenyl and the like; a mono or di(hydroxy)phenyl group such as 2, 3 or 4-hydroxyphenyl, 2,4-dihydroxyphenyl, the protected-hydroxy derivatives thereof and the like; a nitrophenyl group such as 2, 3 or 15 4-nitrophenyl; a cyanophenyl group, for example, 2, 3 or 4-cyanophenyl; a mono- or di(alkyl)phenyl group such as 2, 3 or 4-methylphenyl, 2,4-dimethylphenyl, 2, 3 or 4-(iso-propyl)phenyl, 2, 3 or 4-ethylphenyl, 2, 3 or 4-(n-propyl)phenyl and the like; a mono or 20 di(alkoxyl)phenyl group, for example, 2,6-dimethoxyphenyl, 2, 3 or 4-methoxyphenyl, 2, 3 or 4-ethoxyphenyl, 2, 3 or 4-(isopropoxy)phenyl, 2, 3 or 4-(t-butoxy)phenyl, 3-ethoxy-4-methoxyphenyl and the like; 2, 3 or 4-trifluoromethylphenyl; a mono- or 25 dicarboxyphenyl or (protected carboxy)phenyl group such as 2, 3 or 4-carboxyphenyl or 2,4-di(protected carboxy)phenyl; a mono- or di(hydroxymethyl)phenyl or (protected hydroxymethyl)phenyl such as 2, 3, or 4-(protected hydroxymethyl)phenyl or 30 3,4-di(hydroxymethyl)phenyl; a mono- or di(aminomethyl)phenyl or (protected aminomethyl)phenyl such as 2, 3 or 4-(aminomethyl)phenyl or 2,4-(protected aminomethyl)phenyl; or a mono- or

di(N-(methylsulfonylamino))phenyl such as 2, 3 or 4-(N-(methylsulfonylamino))phenyl. Also, the term "substituted phenyl" represents disubstituted phenyl groups wherein the substituents are different, for example, 3-methyl-4-hydroxyphenyl, 3-chloro-4-hydroxyphenyl, 2-methoxy-4-bromophenyl, 4-ethyl-2-hydroxyphenyl, 3-hydroxy-4-nitrophenyl, 2-hydroxy 4-chlorophenyl and the like.

10 The term "phenoxy" denotes a phenyl bonded to an oxygen atom, wherein the binding to the rest of the molecule is through the oxygen atom. The term "substituted phenoxy" specifies a phenoxy group substituted with one or more, and preferably one or two, 15 moieties chosen from the groups consisting of halogen, hydroxy, protected hydroxy, cyano, nitro, C₁ to C₁₂ alkyl, C₁ to C₁₂ alkoxy, C₁ to C₁₂ substituted alkoxy, C₁ to C₁₂ acyl, C₁ to C₁₂ acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, 20 protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C₁ to C₁₂ alkyl)carboxamide, protected N-(C₁ to C₁₂ alkyl)carboxamide, N, N-di(C₁ to C₁₂ alkyl)carboxamide, 25 trifluoromethyl, N-((C₁ to C₁₂ alkyl)sulfonyl)amino and N-(phenylsulfonyl)amino.

Examples of substituted phenoxy include 2-methylphenoxy, 2-ethylphenoxy, 2-propylphenoxy, 30 2-isopropylphenoxy, 2-sec-butylphenoxy, 2-tert-butylphenoxy, 2-allylphenoxy, 2-propenylphenoxy, 2-cyclopentylphenoxy, 2-fluorophenoxy, 2-(trifluoromethyl)phenoxy, 2-chlorophenoxy,

2-bromophenoxy, 2-methoxyphenoxy, 2-ethoxyphenoxy,
2-isopropoxyphenoxy, 3-methylphenoxy, 3-ethylphenoxy,
3-isopropylphenoxy, 3-tert-butylphenoxy,
3-pentadecylphenoxy, 3-(trifluoromethyl)phenoxy,
5 3-fluorophenoxy, 3-chlorophenoxy, 3-bromophenoxy,
3-iodophenoxy, 3-methoxyphenoxy,
3-(trifluoromethoxy)phenoxy, 4-methylphenoxy,
4-ethylphenoxy, 4-propylphenoxy, 4-isopropylphenoxy,
4-sec-butylphenoxy, 4-tert-butylphenoxy,
10 4-tert-amylphenoxy, 4-nonylphenoxy, 4-dodecylphenoxy,
4-cycloenylphenoxy, 4-(trifluoromethyl)phenoxy,
4-fluorophenoxy, 4-chlorophenoxy, 4-bromophenoxy,
4-iodophenoxy, 4-methoxyphenoxy,
4-(trifluoromethoxy)phenoxy, 4-ethoxyphenoxy,
15 4-propoxyphenoxy, 4-butoxyphenoxy, 4-hexyloxyphenoxy,
4-heptyloxyphenoxy, 2,3-dimethylphenoxy,
5,6,7,8-tetrahydro-1-naphthoxy, 2,3-dichlorophenoxy,
2,3-dihydro-2,2-dimethyl-7-benzofuranoxy,
2,3-dimethoxyphenoxy, 2,6-dimethylphenoxy,
20 2,6-diisopropylphenoxy, 2,6-di-sec-butylphenoxy, 2-tert-
butyl-6-methylphenoxy, 2,6-di-tert-butylphenoxy, 2-allyl-
6-methylphenoxy, 2,6-difluorophenoxy,
2,3-difluorophenoxy, 2,6-dichlorophenoxy,
2,6-dibromophenoxy, 2-fluoro-6-methoxyphenoxy,
25 2,6-dimethoxyphenoxy, 3,5-dimethylphenoxy, 5-isopropyl-
3-methylphenoxy, 3,5-di-tert-butylphenoxy,
3,5-bis(trifluoromethyl)phenoxy, 3,5-difluorophenoxy,
3,5-dichlorophenoxy, 3,5-dimethoxyphenoxy, 3-chloro-5-
methoxyphenoxy, 3,4-dimethylphenoxy, 5-indanoxy,
30 5,6,7,8-tetrahydro-2-naphthoxy, 4-chloro-3-methylphenoxy,
2,4-dimethylphenoxy, 2,5-dimethylphenoxy, 2-isopropyl-
5-methylphenoxy, 4-isopropyl-3-methylphenoxy,
5-isopropyl-2-methylphenoxy, 2-tert-butyl-

5-methylphenoxy, 2-tert-butyl-4-methylphenoxy,
2,4-di-tert-butylphenoxy, 2,4-di-tert-amylphenoxy,
4-fluoro-2-methylphenoxy, 4-fluoro-3-methylphenoxy,
2-chloro-4-methylphenoxy, 2-chloro-5-methylphenoxy,
5 4-chloro-2-methylphenoxy, 4-chloro-3-ethylphenoxy,
2-bromo-4-methylphenoxy, 4-iodo-2-methylphenoxy,
2-chloro-5-(trifluoromethyl)phenoxy, 2,4-difluorophenoxy,
2,5-difluorophenoxy, 3,4-difluorophenoxy; 4-chloro-2-
fluorophenoxy, 3-chloro-4-fluorophenoxy, 4-chloro-3-
10 fluorophenoxy, 2-bromo-4-fluorophenoxy, 4-bromo-2-
fluorophenoxy, 2-bromo-5-fluorophenoxy,
2,4-dichlorophenoxy, 3,4-dichlorophenoxy,
2,5-dichlorophenoxy, 2-bromo-4-chlorophenoxy, 2-chloro-4-
fluorophenoxy, 4-bromo-2-chlorophenoxy,
15 2,4-dibromophenoxy, 2-methoxy-4-methylphenoxy, 4-allyl-2-
methylphenoxy, trans-2-ethoxy-5-(1-propenyl)phenoxy,
2-methoxy-4-propenylphenoxy, 3,4-dimethoxyphenoxy,
3-ethoxy-4-methoxyphenoxy, 4-allyl-2,6-dimethoxyphenoxy,
3,4-methylenedioxyphenoxy, 2,3,6-trimethylphenoxy,
20 2,4-dichloro-3-methylphenoxy, 2,3,4-trifluorophenoxy,
2,3,6-trifluorophenoxy, 2,3,5-trifluorophenoxy,
2,3,4-trichlorophenoxy, 2,3,6-trichlorophenoxy,
2,3,5-trimethylphenoxy, 3,4,5-trimethylphenoxy, 4-chloro-
3,5-dimethylphenoxy, 4-bromo-3,5-dimethylphenoxy,
25 2,4,6-trimethylphenoxy, 2,6-bis(hydroxymethyl)-4-
methylphenoxy, 2,6-di-tert-butyl-4-methylphenoxy, 2,6-
di-tert-butyl-4-methoxyphenoxy, 2,4,5-trifluorophenoxy,
2-chloro-3,5-difluorophenoxy, 2,4,6-trichlorophenoxy,
3,4,5-trimethoxyphenoxy, 2,3,5-trichlorophenoxy, 4-bromo-
30 2,6-dimethylphenoxy, 4-bromo-6-chloro-2-methylphenoxy,
2,6-dibromo-4-methylphenoxy, 2,6-dichloro-4-
fluorophenoxy, 2,6-dibromo-4-fluorophenoxy,
2,4,6-tribromophenoxy, 2,4,6-triiodophenoxy, 2-chloro-

4,5-dimethylphenoxy, 4-chloro-2-isopropyl-5-methylphenoxy, 2-bromo-4,5-difluorophenoxy, 2,4,5-trichlorophenoxy, 2,3,5,6-tetrafluorophenoxy and the like.

5

The term "C₁ to C₁₈ substituted phenylalkoxy" denotes a C₁ to C₁₈ phenylalkoxy group bonded to the rest of the molecule through the oxygen atom, wherein the phenylalkyl portion is substituted with one or more, and preferably one or two, groups selected from halogen, hydroxy, protected hydroxy, oxo, protected oxo, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, guanidino, heterocyclic ring, substituted heterocyclic ring, C₁ to C₁₂ alkoxy, C₁ to C₁₂ acyl, C₁ to C₁₂ acyloxy, nitro, carboxy, protected carboxy, carbamoyl, carboxamide, protected carboxamide, N-(C₁ to C₁₂ alkyl)carboxamide, protected N-(C₁ to C₁₂ alkyl)carboxamide, N, N-(C₁ to C₁₂ dialkyl)carboxamide, cyano, N-(C₁ to C₁₂ alkylsulfonyl)amino, thiol, C₁ to C₁₀ alkylthio, C₁ to C₁₀ alkylsulfonyl groups; and/or the phenyl group can be substituted with one or more, and preferably one or two, substituents chosen from halogen, hydroxy, protected hydroxy, cyano, nitro, C₁ to C₁₂ alkyl, C₁ to C₁₂ alkoxy, C₁ to C₁₂ acyl, C₁ to C₁₂ acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C₁ to C₁₂ alkyl)carboxamide, protected N-(C₁ to C₁₂ alkyl)carboxamide, N, N-di(C₁ to C₁₂ alkyl)carboxamide, trifluoromethyl, N-((C₁ to C₁₂ alkyl)sulfonyl)amino,

N-(phenylsulfonyl)amino or a phenyl group, substituted or unsubstituted, for a resulting biphenyl group. The substituted alkyl or phenyl groups may be substituted with one or more, and preferably one or two, substituents which can be the same or different.

Examples of the term "C₁ to C₁₈-substituted phenylalkoxy" include groups such as 2-(4-hydroxyphenyl)ethoxy, 4-(4-methoxyphenyl)butoxy, (2R)-3-phenyl-2-amino-propoxy, (2S)-3-phenyl-2-amino-propoxy, 10 2-indanoxy, 6-phenyl-1-hexanoxy, cinnamyloxy, (+/-)-2-phenyl-1-propoxy, 2,2-dimethyl-3-phenyl-1-propoxy and the like.

The term "phthalimide" means a cyclic imide which is made from phthalic acid, also called 1,2-benzenedicarboxylic acid. The term "substituted phthalimide" specifies a phthalimide group substituted with one or more, and preferably one or two, moieties chosen from the groups consisting of halogen, hydroxy, 20 protected hydroxy, cyano, nitro, C₁ to C₁₂ alkyl, C₁ to C₁₂ alkoxy, C₁ to C₁₂ substituted alkoxy, C₁ to C₁₂ acyl, C₁ to C₁₂ acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, 25 (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C₁ to C₁₂ alkyl)carboxamide, protected N-(C₁ to C₁₂ alkyl)carboxamide, N, N-di(C₁ to C₁₂ alkyl)carboxamide, trifluoromethyl, N-((C₁ to C₁₂ alkyl)sulfonyl)amino and 30 N-(phenylsulfonyl)amino.

Examples of substituted phthalimides include 4,5-dichlorophthalimido, 3-fluorophthalimido,

4-methoxyphthalimido, 3-methylphthalimido,
4-carboxyphthalimido and the like.

The term "substituted naphthyl" specifies a
5 naphthyl group substituted with one or more, and
preferably one or two, moieties either on the same ring
or on different rings chosen from the groups consisting
of halogen, hydroxy, protected hydroxy, cyano, nitro,
C₁ to C₆ alkyl, C₁ to C₇ alkoxy, C₁ to C₇ acyl, C₁ to C₇
10 acyloxy, carboxy, protected carboxy, carboxymethyl,
protected carboxymethyl, hydroxymethyl, protected
hydroxymethyl, amino, protected amino,
(monosubstituted)amino, protected (monosubstituted)amino,
(disubstituted)amino, carboxamide, protected carboxamide,
15 N-(C₁ to C₁₂ alkyl)carboxamide, protected N-(C₁ to C₁₂
alkyl)carboxamide, N, N-di(C₁ to C₁₂ alkyl)carboxamide,
trifluoromethyl, N-((C₁ to C₁₂ alkyl)sulfonyl)amino or
N-(phenylsulfonyl)amino.

20 Examples of the term "substituted naphthyl"
includes a mono or di(halo)naphthyl group such as 1, 2,
3, 4, 5, 6, 7 or 8-chloronaphthyl, 2, 6-dichloronaphthyl,
2, 5-dichloronaphthyl, 3, 4-dichloronaphthyl, 1, 2, 3, 4,
5, 6, 7 or 8-bromonaphthyl, 3, 4-dibromonaphthyl,
25 3-chloro-4-fluoronaphthyl, 1, 2, 3, 4, 5, 6, 7 or
8-fluoronaphthyl and the like; a mono or
di(hydroxy)naphthyl group such as 1, 2, 3, 4, 5, 6, 7 or
8-hydroxynaphthyl, 2, 4-dihydroxynaphthyl, the protected-
hydroxy derivatives thereof and the like; a nitronaphthyl
30 group such as 3- or 4-nitronaphthyl; a cyanonaphthyl
group, for example, 1, 2, 3, 4, 5, 6, 7 or
8-cyanonaphthyl; a mono- or di(alkyl)naphthyl group such
as 2, 3, 4, 5, 6, 7 or 8-methylnaphthyl, 1, 2,

4-dimethylnaphthyl, 1, 2, 3, 4, 5, 6, 7 or
8-(isopropyl)naphthyl, 1, 2, 3, 4, 5, 6, 7 or
8-ethylnaphthyl, 1, 2, 3, 4, 5, 6, 7 or
8-(n-propyl)naphthyl and the like; a mono or
5 di(alkoxy)naphthyl group, for example, 2,
6-dimethoxynaphthyl, 1, 2, 3, 4, 5, 6, 7 or
8-methoxynaphthyl, 1, 2, 3, 4, 5, 6, 7 or
8-ethoxynaphthyl, 1, 2, 3, 4, 5, 6, 7 or
8-(isopropoxy)naphthyl, 1, 2, 3, 4, 5, 6, 7 or
10 8-(t-butoxy)naphthyl, 3-ethoxy-4-methoxynaphthyl and the
like; 1, 2, 3, 4, 5, 6, 7 or 8-trifluoromethylnaphthyl; a
mono- or dicarboxynaphthyl or (protected carboxy)naphthyl
group such as 1, 2, 3, 4, 5, 6, 7 or 8-carboxynaphthyl or
2, 4-di(-protected carboxy)naphthyl; a mono- or
15 di(hydroxymethyl)naphthyl or (protected
hydroxymethyl)naphthyl such as 1, 2, 3, 4, 5, 6, 7 or
8-(protected hydroxymethyl)naphthyl or 3,
4-di(hydroxymethyl)naphthyl; a mono- or di(amino)naphthyl
or (protected amino)naphthyl such as 1, 2, 3, 4, 5, 6, 7
20 or 8-(amino)naphthyl or 2, 4-(protected amino)-naphthyl,
a mono- or di(aminomethyl)naphthyl or (protected
aminomethyl)naphthyl such as 2, 3, or
4-(aminomethyl)naphthyl or 2, 4-(protected aminomethyl)-
naphthyl; or a mono- or di-(N-methylsulfonylamino)
25 naphthyl such as 1, 2, 3, 4, 5, 6, 7 or
8-(N-methylsulfonylamino)naphthyl. Also, the term
"substituted naphthyl" represents disubstituted naphthyl
groups wherein the substituents are different, for
example, 3-methyl-4-hydroxynaphth-1-yl, 3-chloro-4-
30 hydroxynaphth-2-yl, 2-methoxy-4-bromonaphth-1-yl,
4-ethyl-2-hydroxynaphth-1-yl, 3-hydroxy-4-nitronaphth-2-
yl, 2-hydroxy-4-chloronaphth-1-yl, 2-methoxy-7-
bromonaphth-1-yl, 4-ethyl-5-hydroxynaphth-2-yl,

3-hydroxy-8-nitronaphth-2-yl, 2-hydroxy-5-chloronaphth-1-yl and the like.

The term "naphthylene" means a naphthyl radical
5 bonded at two positions connecting together two separate
additional groups. Similarly, the term "substituted
naphthylene" means a naphthylene group that is further
substituted by halogen, hydroxy, protected hydroxy, C₁ to
C₁₀ alkylthio, C₁ to C₁₀ alkylsulfoxide, C₁ to C₁₀
10 alkylsulfonyl, C₁ to C₁₀ substituted alkylthio, C₁ to C₁₀
substituted alkylsulfoxide, C₁ to C₁₀ substituted
alkylsulfonyl, C₁ to C₁₂ alkyl, C₁ to C₁₂ alkoxy, C₁ to C₁₂
substituted alkyl, C₁ to C₁₂ alkoxy, oxo, protected oxo,
(monosubstituted)amino, (disubstituted)amino,
15 trifluoromethyl, carboxy, protected carboxy, phenyl,
substituted phenyl, phenylthio, phenylsulfoxide,
phenylsulfonyl, amino, or protected amino group.

The terms "halo" and "halogen" refer to the
20 fluoro, chloro, bromo or iodo atoms. There can be one or
more halogens, which are the same or different.
Preferred halogens are chloro and fluoro.

The term "(monosubstituted)amino" refers to an
25 amino group with one substituent chosen from the group
consisting of phenyl, substituted phenyl, C₁ to C₁₂ alkyl,
C₁ to C₁₂ substituted alkyl, C₁ to C₁₂ acyl, C₁ to C₁₂
substituted acyl, C₂ to C₁₂ alkenyl, C₂ to C₁₂ substituted
alkenyl, C₂ to C₁₂ alkynyl, C₂ to C₁₂ substituted alkynyl,
30 C₇ to C₁₈ phenylalkyl, C₇ to C₁₈ substituted phenylalkyl,
heterocyclic ring, substituted heterocyclic ring, C₁ to
C₁₂ heterocycloalkyl and C₁ to C₁₂ substituted
heterocycloalkyl. The (monosubstituted)amino can

additionally have an amino-protecting group as encompassed by the term "protected (monosubstituted)amino."

5 The term "(disubstituted)amino" refers to an amino group with two substituents chosen from the group consisting of phenyl, substituted phenyl, C₁ to C₁₂ alkyl, C₁ to C₁₂ substituted alkyl, C₁ to C₁₂ acyl, C₂ to C₁₂ alkenyl, C₂ to C₁₂ alkynyl, C₇ to C₁₈ phenylalkyl, C₇ to C₁₈ 10 substituted phenylalkyl, C₁ to C₁₂ heterocycloalkyl and C₁ to C₁₂ substituted heterocycloalkyl. The two substituents can be the same or different.

15 The term "amino-protecting group" as used herein refers to substituents of the amino group commonly employed to block or protect the amino functionality while reacting other functional groups of the molecule. The term "protected (monosubstituted)amino" means there is an amino-protecting group on the monosubstituted amino 20 nitrogen atom. In addition, the term "protected carboxamide" means there is an amino-protecting group on the carboxamide nitrogen. Similarly, the term "protected N-(C₁ to C₁₂ alkyl)carboxamide" means there is an amino-protecting group on the carboxamide nitrogen.

25 Examples of such amino-protecting groups. include the formyl ("For") group, the trityl group, the phthalimido group, the trichloroacetyl group, the chloroacetyl, bromoacetyl, and iodoacetyl groups, 30 urethane-type blocking groups, such as t-butoxycarbonyl ("Boc"), 2-(4-biphenyl)propyl-2-oxycarbonyl ("Bpoc"), 2-phenylpropyl-2-oxycarbonyl ("Poc"), 2-(4-xenyl)isopropoxycarbonyl, 1,1-diphenylethyl-1-

oxycarbonyl, 1,1-diphenylpropyl-1-oxycarbonyl, 2-(3,5-dimethoxyphenyl)propyl-2-oxycarbonyl ("Ddz"), 2-(p-toluyl)propyl-2-oxycarbonyl, cyclopentanyloxycarbonyl, 1-methylcyclopentanyloxycarbonyl, cyclohexanyloxy-
5 carbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-tolylsulfonyl)-ethoxycarbonyl, 2-(methylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphino)-ethoxycarbonyl, 9-fluorenylmethoxycarbonyl ("Fmoc"),
10 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzyl-oxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl,
15 isobornyloxycarbonyl, 1-piperidyloxycarbonyl, benzyloxycarbonyl ("Cbz"), 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxy-carbonyl, -2,4,5,- tetramethylbenzyloxycarbonyl ("Tmz"), 4-methoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl,
20 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyl-oxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxy-carbonyl, 4-cyanobenzyloxycarbonyl, 4-(decyloxy)benzyloxycarbonyl
25 and the like; the benzoylmethylsulfonyl group, dithiasuccinoyl ("Dts"), the 2-(nitro)phenylsulfenyl group ("Nps"), the diphenyl-phosphine oxide group and like amino-protecting groups. The species of amino-protecting group employed is not critical so long as the
30 derivatized amino group is stable to the conditions of the subsequent reaction(s) and can be removed at the appropriate point without disrupting the remainder of the compounds. Preferred amino-protecting groups are Boc,

Cbz and Fmoc. Further examples of amino-protecting groups embraced by the above term are well known in organic synthesis and the peptide art and are described by, for example, T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," 2nd ed., John Wiley and Sons, New York, NY, 1991, Chapter 7, M. Bodanzsky, "Principles of Peptide Synthesis," 1st and 2nd revised ed., Springer-Verlag, New York, NY, 1984 and 1993, and Stewart and Young, "Solid Phase Peptide Synthesis," 2nd ed., Pierce Chemical Co., Rockford, IL, 1984, each of which is incorporated herein by reference. The related term "protected amino" defines an amino group substituted with an amino-protecting group discussed above.

15 The term "protected guanidino" as used herein refers to an "amino-protecting group" on one or two of the guanidino nitrogen atoms. Examples of "protected guanidino" groups are described by T.W. Greene and P.G.M. Wuts; M. Bodanzsky; and Stewart and Young, *supra*.

20 25 The term "epimino" means $-\text{NH}-$. The term "substituted epimino" means $-\text{N}(\text{R})-$, where R is a substitution group listed above under the definition of "(monosubstituted)amino."

25 The term "C₁ to C₅ alkylene epimino" refers to a one to five carbon alkylene chain with an epimino at any point along the chain. The term "C₁ to C₅ substituted alkylene epimino" refers to a C₁ to C₅ alkylene epimino group that is substituted a) at the epimino position (in the same way as "substituted epimino," described above); and/or b) at one or more of the alkylene positions (in

the same way as "substituted alkylene," as described above).

The term "thio" refers to -SH or, if between
5 two other groups, -S-. The term "C₁ to C₁₀ alkylene thio" refers to a one to ten carbon alkylene chain with a thio at any point along the chain. The term "C₁ to C₁₀ substituted alkylene thio" refers to a C₁ to C₁₀ alkylene thio group that is substituted at one or more of the
10 alkylene positions (in the same way as "substituted alkylene," as described above).

The term "sulfonyl" refers to -S(O)₂-. The term "C₁ to C₁₀ alkylene sulfonyl" refers to a one to ten
15 carbon alkylene chain with a sulfonyl at any point along the chain. The term "C₁ to C₁₀ substituted alkylene sulfonyl" refers to a C₁ to C₁₀ alkylene sulfonyl group that is substituted at one or more of the alkylene positions (in the same way as "substituted alkylene," as
20 described above).

The term "sulfinyl" refers to -S(O)-. The term "C₁ to C₁₀ alkylene sulfinyl" refers to a one to ten carbon alkylene chain with a sulfinyl at any point along
25 the chain. The term "C₁ to C₁₀ substituted alkylene sulfinyl" refers to a C₁ to C₁₀ alkylene sulfinyl group that is substituted at one or more of the alkylene positions (in the same way as "substituted alkylene," as described above).

The term "oxy" refers to -O-. The terms "C₁ to C₁₀ alkylene oxy," "C₁ to C₁₀ alkylene dioxy" and "C₁ to C₁₀ alkylene trioxy" refer to a one to ten carbon alkylene

chain with, respectively, one, two or three -O- at any point along the chain, provided that no two oxygen atoms are consecutive, and provided that any two oxygen atoms are separated by at least two carbons. The terms "C₁ to 5 C₁₀ substituted alkylene oxy," "C₁ to C₁₀ substituted alkylene dioxy" and "C₁ to C₁₀ substituted alkylene trioxy" refer, respectfully to "C₁ to C₁₀ alkylene oxy," "C₁ to C₁₀ alkylene dioxy" and "C₁ to C₁₀ alkylene trioxy" 10 that are substituted at one or more of the alkylene positions (in the same way as "substituted alkylene," as described above).

The term "thiocarbonyl" refers to -C(S)H or, if between two other groups, -C(S)-. The term "thioester" 15 refers to -C(O)SH or, if between two other groups, -C(O)S-.

The term "carboxy-protecting group" as used herein refers to one of the ester derivatives of the 20 carboxylic acid group commonly employed to block or protect the carboxylic acid group while reactions are carried out on other functional groups on the compound. Examples of such carboxylic acid protecting groups 25 include t-butyl, 4-nitrobenzyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, pentamethylbenzyl, 3,4-methylenedioxybenzyl, benzhydryl, 4,4'-dimethoxytrityl, 4,4',4"-trimethoxytrityl, 30 2-phenylpropyl, trimethylsilyl, t-butyldimethylsilyl, phenacyl, 2,2,2-trichloroethyl, (trimethylsilyl)ethyl, (di(n-butyl)methylsilyl)ethyl, p-toluenesulfonylethyl, 4-nitrobenzylsulfonylethyl, allyl, cinnamyl, 1-(trimethylsilylmethyl)propenyl and like moieties. The

species of carboxy-protecting group employed is not critical so long as the derivatized carboxylic acid is stable to the conditions of subsequent reaction(s) and can be removed at the appropriate point without disrupting the remainder of the molecule. Further examples of these groups are found in E. Haslam, "Protective Groups in Organic Chemistry," J.G.W. McOmie, Ed., Plenum Press, New York, NY, 1973, Chapter 5, and T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," 2nd ed., John Wiley and Sons, New York, NY, 1991, Chapter 5, each of which is incorporated herein by reference. A related term is "protected carboxy," which refers to a carboxy group substituted with one of the above carboxy-protecting groups.

15

The term "hydroxy-protecting group" refers to readily cleavable groups bonded to hydroxyl groups, such as the tetrahydropyranyl, 2-methoxypropyl, 1-ethoxyethyl, methoxymethyl, 2-methoxyethoxymethyl, methylthiomethyl, t-butyl, t-amyl, trityl, 4-methoxytrityl, 4,4'-dimethoxytrityl, 4,4',4"-trimethoxytrityl, benzyl, allyl, trimethylsilyl, (t-butyl)dimethylsilyl, 2,2,2-trichloroethoxycarbonyl groups and the like. The species of hydroxy-protecting groups is not critical so long as the derivatized hydroxyl group is stable to the conditions of subsequent reaction(s) and can be removed at the appropriate point without disrupting the remainder of the molecule. Further examples of hydroxy-protecting groups are described by C.B. Reese and E. Haslam, "Protective Groups in Organic Chemistry," J.G.W. McOmie, Ed., Plenum Press, New York, NY, 1973, Chapters 3 and 4, respectively, and T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," 2nd ed., John

Wiley and Sons, New York, NY, 1991, Chapters 2 and 3. Related terms are "protected hydroxy," and "protected hydroxymethyl" which refer to a hydroxy or hydroxymethyl substituted with one of the above hydroxy-protecting groups.

- The term "C₁ to C₁₀ alkylthio" refers to sulfide groups such as methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, t-butylthio and like groups.

10 The term "C₁ to C₁₀ alkylsulfoxide" indicates sulfoxide groups such as methylsulfoxide, ethylsulfoxide, n-propylsulfoxide, isopropylsulfoxide, n-butylsulfoxide, sec-butylsulfoxide and the like. The term "C₁ to C₁₀ alkylsulfonyl" encompasses groups such as methylsulfonyl, 15 ethylsulfonyl, n-propylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, t-butylsulfonyl and the like. It should also be understood that the above thio, sulfoxide or sulfonyl groups can be at any point on the alkyl chain (e.g., 2-methylmercaptoethyl).

20

The terms "C₁ to C₁₀ substituted alkylthio," "C₁ to C₁₀ substituted alkylsulfoxide," and "C₁ to C₁₀ substituted alkylsulfonyl," denote the C₁ to C₁₀ alkyl portion of these groups may be substituted as described 25 above in relation to "substituted alkyl."

The terms "phenylthio," "phenylsulfoxide," and "phenylsulfonyl" specify a thiol, a sulfoxide, or sulfone, respectively, containing a phenyl group. The 30 terms "substituted phenylthio," "substituted phenylsulfoxide," and "substituted phenylsulfonyl" means that the phenyl of these groups can be substituted as described above in relation to "substituted phenyl."

The term "C₁ to C₁₂ alkylaminocarbonyl" means a C₁ to C₁₂ alkyl attached to a nitrogen of the aminocarbonyl group. Examples of C₁ to C₁₂ alkylaminocarbonyl include methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl and butylaminocarbonyl. The term "C₁ to C₁₂ substituted alkylaminocarbonyl" denotes a substituted alkyl bonded to a nitrogen of the aminocarbonyl group, which alkyl may be substituted as described above in relation to C₁ to C₁₂ substituted alkyl. Examples of C₁ to C₁₂ substituted alkylaminocarbonyl include, for example, methoxymethylaminocarbonyl, 2-chloroethylaminocarbonyl, 2-oxopropylaminocarbonyl and 4-phenylbutylaminocarbonyl.

15

The term "C₁ to C₁₂ alkoxy carbonyl" means a "C₁ to C₁₂ alkoxy" group attached to a carbonyl group. The term "C₁ to C₁₂ substituted alkoxy carbonyl" denotes a substituted alkoxy bonded to the carbonyl group, which alkoxy may be substituted as described above in relation to "C₁ to C₁₂ substituted alkyl."

The term "phenylaminocarbonyl" means a phenyl attached to a nitrogen of the aminocarbonyl group. The term "substituted phenylaminocarbonyl" denotes a substituted phenyl bonded to a nitrogen of the aminocarbonyl group, which phenyl may be substituted as described above in relation to substituted phenyl. Examples of substituted phenylaminocarbonyl include 2-chlorophenylaminocarbonyl, 3-chlorophenylaminocarbonyl, 2-nitrophenylaminocarbonyl, 4-biphenylaminocarbonyl, and 4-methoxyphenylaminocarbonyl.

The term "C₁ to C₁₂ alkylaminothiocarbonyl" means a C₁ to C₁₂ alkyl attached to an aminothiocarbonyl group, wherein the alkyl has the same meaning as defined above. Examples of C₁ to C₁₂ alkylaminothiocarbonyl 5 include methylaminothiocarbonyl, ethylaminothiocarbonyl, propylaminothiocarbonyl and butylaminothiocarbonyl.

The term "C₁ to C₁₂ substituted alkylaminothiocarbonyl" denotes a substituted alkyl 10 bonded to an aminothiocarbonyl group, wherein the alkyl may be substituted as described above in relation to C₁ to C₁₂ substituted alkyl. Examples of C₁ to C₁₂ substituted alkylaminothiocarbonyl include, for example, methoxymethylaminothiocarbonyl, 15 2-chloroethylaminothiocarbonyl, 2-oxopropylaminothiocarbonyl and 4-phenylbutylaminothiocarbonyl.

The term "phenylaminothiocarbonyl" means a 20 phenyl attached to an aminothiocarbonyl group, wherein the phenyl has the same meaning as defined above.

The term "substituted phenylaminothiocarbonyl" denotes a substituted phenyl bonded to an 25 aminothiocarbonyl group, wherein phenyl may be substituted as described above in relation to substituted phenyl. Examples of substituted phenylaminothiocarbonyls include 2-chlorophenylaminothiocarbonyl, 3-chlorophenylaminothiocarbonyl, 30 2-nitrophenylaminothiocarbonyl, 4-biphenylaminothiocarbonyl and 4-methoxyphenylaminothiocarbonyl.

The term "phenylene" means a phenyl group where the phenyl radical is bonded at two positions connecting together two separate additional groups. Examples of "phenylene" include 1,2-phenylene, 1,3-phenylene, and

5 1,4-phenylene.

- The term "substituted phenylene" means a phenyl group where the phenyl radical is bonded at two positions connecting together two separate additional groups,

10 wherein the phenyl is substituted as described above in relation to "substituted phenyl."

The term "substituted C₁ to C₁₂ alkylene" means a C₁ to C₁₂ alkyl group where the alkyl radical is bonded

15 at two positions connecting together two separate

additional groups and further bearing an additional

substituent. Examples of "substituted C₁ to C₁₂ alkylene" includes aminomethylene, 1-(amino)-1,2-ethyl, 2-(amino)-

1,2-ethyl, 1-(acetamido)-1,2-ethyl, 2-(acetamido)-1,2-

20 ethyl, 2-hydroxy-1,1-ethyl, 1-(amino)-1,3-propyl.

The terms "cyclic C₂ to C₇ alkylene," "substituted cyclic C₂ to C₇ alkylene," "cyclic C₂ to C₇ heteroalkylene," and "substituted cyclic C₂ to C₇ heteroalkylene," defines such a cyclic group bonded

25 ("fused") to the phenyl radical resulting in a bicyclic ring system. The cyclic group may be saturated or

contain one or two double bonds. Furthermore, the cyclic

group may have one or two methylene or methine groups

30 replaced by one or two oxygen, nitrogen or sulfur atoms which are the cyclic C₂ to C₇ heteroalkylene.

The cyclic alkylene or heteroalkylene group may be substituted once or twice by the same or different substituents which, if appropriate, can be connected to another part of the compound (e.g., alkylene) selected 5 from the group consisting of the following moieties: hydroxy, protected hydroxy, carboxy, protected carboxy, oxo, protected oxo, C₁ to C₄ acyloxy, formyl, C₁ to C₁₂ acyl, C₁ to C₁₂ alkyl, C₁ to C₇ alkoxy, C₁ to C₁₀ alkylthio, C₁ to C₁₀ alkylsulfoxide, C₁ to C₁₀ alkylsulfonyl, halo, 10 amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, hydroxymethyl or a protected hydroxymethyl.

The cyclic alkylene or heteroalkylene group 15 fused onto the benzene radical can contain two to ten ring members, but it preferably contains three to six members. Examples of such saturated cyclic groups are when the resultant bicyclic ring system is 2,3-dihydro-indanyl and a tetralin ring. When the cyclic groups are 20 unsaturated, examples occur when the resultant bicyclic ring system is a naphthyl ring or indolyl. Examples of fused cyclic groups which each contain one nitrogen atom and one or more double bond, preferably one or two double bonds, are when the benzene radical is fused to a 25 pyridino, pyrano, pyrrolo, pyridinyl, dihydropyrrolo, or dihydropyridinyl ring. Examples of fused cyclic groups which each contain one oxygen atom and one or two double bonds are when the benzene radical ring is fused to a furo, pyrano, dihydrofuran, or dihydropyran ring. 30 Examples of fused cyclic groups which each have one sulfur atom and contain one or two double bonds are when the benzene radical is fused to a thieno, thiopyrano, dihydrothieno or dihydrothiopyrano ring. Examples of

cyclic groups which contain two heteroatoms selected from sulfur and nitrogen and one or two double bonds are when the benzene radical ring is fused to a thiazolo, isothiazolo, dihydrothiazolo or dihydroisothiazolo ring.

5 Examples of cyclic groups which contain two heteroatoms selected from oxygen and nitrogen and one or two double bonds are when the benzene ring is fused to an oxazolo, isoxazolo, dihydrooxazolo or dihydroisoxazolo ring.

Examples of cyclic groups which contain two nitrogen

10 heteroatoms and one or two double bonds occur when the benzene ring is fused to a pyrazolo, imidazolo, dihydropyrazolo or dihydroimidazolo ring or pyrazinyl.

The term "carbamoyl" means an -NC(O)- group

15 where the radical is bonded at two positions connecting two separate additional groups.

One or more of the compounds of the invention, even within a given library, may be present as a salt.

20 The term "salt" encompasses those salts that form with the carboxylate anions and amine nitrogens and include salts formed with the organic and inorganic anions and cations discussed below. Furthermore, the term includes salts that form by standard acid-base reactions with

25 basic groups (such as amino groups) and organic or inorganic acids. Such acids include hydrochloric, hydrofluoric, trifluoroacetic, sulfuric, phosphoric, acetic, succinic, citric, lactic, maleic, fumaric, palmitic, cholic, pamoic, mucic, D-glutamic, D-camphoric,

30 glutaric, phthalic, tartaric, lauric, stearic, salicyclic, methanesulfonic, benzenesulfonic, sorbic, picric, benzoic, cinnamic, and like acids.

The term "organic or inorganic cation" refers to counter-ions for the carboxylate anion of a carboxylate salt. The counter-ions are chosen from the alkali and alkaline earth metals, (such as lithium, 5 sodium, potassium, barium, aluminum and calcium); ammonium and mono-, di- and tri-alkyl amines such as trimethylamine, cyclohexylamine; and the organic cations, such as dibenzylammonium, benzylammonium, 2-hydroxyethylammonium, bis(2-hydroxyethyl)ammonium, 10 phenylethylbenzylammonium, dibenzylethylenediammonium, and like cations. See, for example, "Pharmaceutical Salts," Berge et al., J. Pharm. Sci., 66:1-19 (1977), which is incorporated herein by reference. Other cations encompassed by the above term include the protonated form 15 of procaine, quinine and N-methylglucosamine, and the protonated forms of basic amino acids such as glycine, ornithine, histidine, phenylglycine, lysine and arginine. Furthermore, any zwitterionic form of the instant compounds formed by a carboxylic acid and an amino group 20 is referred to by this term. For example, a cation for a carboxylate anion will exist when a position is substituted with a (quaternary ammonium)methyl group. A preferred cation for the carboxylate anion is the sodium cation.

25

The compounds of the invention can also exist as solvates and hydrates. Thus, these compounds may crystallize with, for example, waters of hydration, or one, a number of, or any fraction thereof of molecules of 30 the mother liquor solvent. The solvates and hydrates of such compounds are included within the scope of this invention.

One or more compounds of the invention, even when in a library, can be in the biologically active ester form, such as the non-toxic, metabolically-labile ester-form. Such ester forms induce increased blood 5 levels and prolong the efficacy of the corresponding non-esterified forms of the compounds. Ester groups which can be used include the lower alkoxyethyl groups, for example, methoxymethyl, ethoxymethyl, isopropoxymethyl and the like; the -(C₁ to C₁₂) alkoxyethyl groups, for 10 example methoxyethyl, ethoxyethyl, propoxyethyl, isopropoxyethyl and the like; the 2-oxo-1,3-dioxolen-4-ylmethyl groups, such as 5-methyl-2-oxo-1,3-dioxolen-4-ylmethyl, 5-phenyl-2-oxo-1,3-dioxolen-4-ylmethyl and the like; the C₁ to C₁₀ alkylthiomethyl groups, for example 15 methylthiomethyl, ethylthiomethyl, iso-propylthiomethyl and the like; the acyloxymethyl groups, for example pivaloyloxymethyl, pivaloyloxyethyl, -acetoxyethyl and the like; the ethoxycarbonyl-1-methyl group; the -acetoxyethyl; the 1-(C₁ to C₁₂) alkylaminocarbonyloxyethyl groups such as the 1-(ethoxycarbonyloxyethyl group; and the 1-(C₁ to C₁₂) alkylaminocarbonyloxyethyl groups such 20 as the 1-(methylaminocarbonyloxyethyl group.

The term "amino acid" includes any one of the 25 twenty naturally-occurring amino acids or the D-form of any one of the naturally-occurring amino acids. In addition, the term "amino acid" also includes other non-naturally occurring amino acids besides the D-amino acids, which are functional equivalents of the naturally- 30 occurring amino acids. Such non-naturally-occurring amino acids include, for example, norleucine ("Nle"), norvaline ("Nva"), L- or D- naphthalanine, ornithine ("Orn"), homoarginine (homoArg) and others well known in

the peptide art, such as those described in M. Bodanzsky, "Principles of Peptide Synthesis," 1st and 2nd revised ed., Springer-Verlag, New York, NY, 1984 and 1993, and Stewart and Young, "Solid Phase Peptide Synthesis," 2nd 5 ed., Pierce Chemical Co., Rockford, IL, 1984, both of which are incorporated herein by reference. Amino acids and amino-acid analogs can be purchased commercially (Sigma Chemical Co.; Advanced Chemtech) or synthesized using methods known in the art.

10

It should be understood that any position of the claimed invention has up to three serial "substitutions." For example, a "substituted alkyl" that is substituted with a "substituted phenyl" that is, in 15 turn, substituted with a "substituted alkyl" can, in turn, be substituted by one more group and no longer further substituted. However, it should also be understood that the invention contemplates, if appropriate, more than three parallel substitutions. 20 For example, if appropriate, more than three hydrogens on an alkyl moiety may be substituted with any one or more of a variety of groups, including halo and hydroxy.

The term "functionalized resin" means any 25 resin, crosslinked or otherwise, where functional groups have been introduced into the resin, as is common in the art. Such resins include, for example, those functionalized with amino, alkylhalo, formyl or hydroxy groups. Such resins which can serve as solid supports 30 are well known in the art and include, for example, 4-methylbenzhydrylamine-copoly(styrene-1% divinylbenzene) (MBHA), 4-hydroxymethylphenoxyethyl-copoly(styrene-1% divinylbenzene), 4-oxymethyl-phenyl-acetamido-

copoly(styrene-1% divinylbenzene) (Wang), 4-(oxymethyl)-phenylacetamido methyl (Pam), and Tentagel™, from Rapp Polymere GmbH, trialkoxy-diphenyl-methyl ester-copoly(styrene-1% divinylbenzene) (RINK) all of which are 5 commercially available. Other functionalized resins are known in the art and can be used without departure from the scope of the current invention. Such resins may include those described in Jung, G., Combinatorial Peptide and Nonpeptide Libraries, A Handbook (VCH Verlag, 10 1996) or Bunin, B. A., The Combinatorial Index (Academic Press, 1998) and are incorporated herein by reference.

As used herein, a "combinatorial library" is an intentionally created collection of differing molecules 15 which can be prepared by the means provided below or otherwise and screened for biological activity in a variety of formats (e.g., libraries of soluble molecules, libraries of compounds attached to resin beads, silica chips or other solid supports). A "combinatorial 20 library," as defined above, involves successive rounds of chemical syntheses based on a common starting structure. The combinatorial libraries can be screened in any variety of assays, such as those detailed below as well as others useful for assessing their biological activity. 25 The combinatorial libraries will generally have at least one active compound and are generally prepared such that the compounds are in equimolar quantities.

Compounds disclosed in previous work that are 30 not disclosed as part of a collection of compounds or not disclosed as intended for use as part of such a collection are not part of a "combinatorial library" of the invention. In addition, compounds that are in an

unintentional or undesired mixture are not part of a "combinatorial library" of the invention.

A combinatorial library of the invention can
5 contain two or more of the above-described compounds. The invention further provides a combinatorial library containing three, four or five or more of the above-described compounds. In another embodiment of the invention, a combinatorial library can contain ten or
10 more of the above-described compounds. In yet another embodiment of the invention, a combinatorial library can contain fifty or more of the above-described compounds. If desired, a combinatorial library of the invention can contain 100,000 or more, or even 1,000,000 or more, of
15 the above-described compounds.

By way of example, the preparation of the combinatorial libraries can use the "split resin approach." The split resin approach is described by, for
20 example, U.S. Patent 5,010,175 to Rutter, WO PCT 91/19735 to Simon, and Gallop et al., *J. Med. Chem.*, 37:1233-1251 (1994), all of which are incorporated herein by reference.

25 The amino acids are indicated herein by either their full name or by the commonly known three letter code. Further, in the naming of amino acids, "D-" designates an amino acid having the "D" configuration, as opposed to the naturally occurring L-amino acids. Where
30 no specific configuration is indicated, one skilled in the art would understand the amino acid to be an L-amino acid. The amino acids can, however, also be in racemic mixtures of the D- and L-configuration or the D-amino

acid can readily be substituted for that in the L-configuration.

For preparing pharmaceutical compositions containing compounds of the invention, inert, pharmaceutically acceptable carriers are used. The pharmaceutical carrier can be either solid or liquid. Solid form preparations include, for example, powders, tablets, dispersible granules, capsules, cachets, and 10 suppositories.

A solid carrier can be one or more substances which can also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or 15 tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is generally a finely divided solid which is in a mixture with the finely 20 divided active component. In tablets, the active compound is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

25 For preparing pharmaceutical composition in the form of suppositories, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten 30 homogeneous mixture is then poured into convenient-sized molds and allowed to cool and solidify.

Powders and tablets preferably contain between about 5% to about 70% by weight of the active ingredient. Suitable carriers include, for example, magnesium carbonate, magnesium stearate, talc, lactose, sugar, 5 pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter and the like.

The pharmaceutical compositions can include the 10 formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier, which is thus in association with it. In a similar manner, cachets are also included. 15 Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid pharmaceutical compositions include, for example, solutions suitable for oral or parenteral 20 administration, or suspensions, and emulsions suitable for oral administration. Sterile water solutions of the active component or sterile solutions of the active component in solvents comprising water, ethanol, or propylene glycol are examples of liquid compositions 25 suitable for parenteral administration.

Sterile solutions can be prepared by dissolving the active component in the desired solvent system, and then passing the resulting solution through a membrane 30 filter to sterilize it or, alternatively, by dissolving the sterile compound in a previously sterilized solvent under sterile conditions.

Aqueous solutions for oral administration can be prepared by dissolving the active compound in water and adding suitable flavorants, coloring agents, stabilizers, and thickening agents as desired. Aqueous 5 suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural or synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical 10 formulation art.

Preferably, the pharmaceutical composition is in unit dosage form. In such form, the composition is divided into unit doses containing appropriate quantities 15 of the active 2-aminobenzoxazole compound. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparation, for example, packeted tablets, capsules, and powders in vials or ampules. The unit dosage form can also be a capsule, 20 cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

As pharmaceutical compositions for treating infections, pain, or any other indication the compounds 25 of the present invention are generally in a pharmaceutical composition so as to be administered to a subject at dosage levels of from 0.7 to 7000 mg per day, and preferably 1 to 500 mg per day, for a normal human adult of approximately 70 kg of body weight, this 30 translates into a dosage of from 0.01 to 100 mg/kg of body weight per day. The specific dosages employed, however, can be varied depending upon the requirements of the patient, the severity of the condition being treated,

and the activity of the compound being employed. The determination of optimum dosages for a particular situation is within the skill of the art.

5 2-aminobenzoxazole derivative compounds and libraries, such as those of the present invention, can be made utilizing individual polyethylene bags, referred to as "tea bags" (see Houghten et al., *Proc. Natl. Acad. Sci. USA* 82: 5131 (1985); *Biochemistry*, 32:11035 (1993);
10 and U.S. Patent No. 4,631,211, all of which are incorporated herein by reference).

The nonsupport-bound combinatorial libraries can be screened as single compounds. In addition, the
15 nonsupport-bound combinatorial libraries can be screened as mixtures in solution in assays such as radio-receptor inhibition assays, anti-bacterial assays, anti-fungal assays, calmodulin-dependent phosphodiesterase (CaMPDE) assays and phosphodiesterase (PDE) assays, as described
20 in detail below. Deconvolution of highly active mixtures can then be carried out by iterative or positional scanning methods. These techniques, the iterative approach or the positional scanning approach, can be utilized for finding other active compounds within the
25 combinatorial libraries of the present invention using any one of the below-described assays or others well known in the art.

The iterative approach is well-known and is set
30 forth in general in Houghten et al., *Nature*, 354, 84-86 (1991) and Dooley et al., *Science*, 266, 2019-2022 (1994), both of which are incorporated herein by reference. In the iterative approach, for example, sub-libraries of a

molecule having three variable groups are made wherein the first variable is defined. Each of the compounds with the defined variable group is reacted with all of the other possibilities at the other two variable groups.

5 These sub-libraries are each tested to define the identity of the second variable in the sub-library having the highest activity in the screen of choice. A new sub-library with the first two variable positions defined is reacted again with all the other possibilities at the
10 remaining undefined variable position. As before, the identity of the third variable position in the sub-library having the highest activity is determined. If more variables exist, this process is repeated for all variables, yielding the compound with each variable
15 contributing to the highest desired activity in the screening process. Promising compounds from this process can then be synthesized on larger scale in traditional single-compound synthetic methods for further biological investigation.

20

The positional-scanning approach has been described for various combinatorial libraries as described, for example, in R. Houghten et al. PCT/US91/08694 and U.S. Patent 5,556,762, both of which
25 are incorporated herein by reference. In the positional scanning approach, sublibraries are made defining only one variable with each set of sublibraries and all possible sublibraries with each single variable defined (and all other possibilities at all of the other variable
30 positions), made and tested. From the instant description one skilled in the art could synthesize combinatorial libraries wherein two fixed positions are defined at a time. From the testing of each single-

variable defined combinatorial library, the optimum substituent at that position can be determined, pointing to the optimum or at least a series of compounds having a maximum of the desired biological activity. Thus, the 5 number of sublibraries for compounds with a single position defined will be the number of different substituents desired at that position, and the number of all the compounds in each sublibrary will be the product of the number of substituents at each of the other 10 variables.

Individual compounds and pharmaceutical compositions containing the compounds, as well as methods of using the same, are included within the scope of the 15 present invention. The compounds of the present invention can be used for a variety of purposes and indications and as medicaments for any such purposes and indications. For example, 2-aminobenzoxazole derivative compounds of the present invention can be used as 20 pesticides, acaricides, receptor agonists or antagonists and antimicrobial agents, including antibacterial or antiviral agents. The libraries can be screened in any variety of melanocortin receptor and related activity assays, such as those detailed below as well as others 25 known in the art. Additionally, the subject compounds can be useful as analgesics. Assays which can be used to test the biological activity of the instant compounds include antimicrobial assays, a competitive enzyme-linked immunoabsorbent assay and radio-receptor assays, as 30 described below.

The melanocortin (MC) receptors are a group of cell surface proteins that mediate a variety of

physiological effects, including regulation of adrenal gland function such as production of the glucocorticoids cortisol and aldosterone; control of melanocyte growth and pigment production; thermoregulation; 5 immunomodulation; and analgesia. Five distinct MC receptors have been cloned and are expressed in a variety of tissues, including melanocytes, adrenal cortex, brain, gut, placenta, skeletal muscle, lung, spleen, thymus, bone marrow, pituitary, gonads and 10 adipose tissue (Tatro, Neuroimmunomodulation 3:259-284 (1996)). Three MC receptors, MCR-1, MCR-3 and MCR-4, are expressed in brain tissue (Xia et al., Neuroreport 6:2193-2196 (1995)).

15 A variety of ligands termed melanocortins function as agonists that stimulate the activity of MC receptors. The melanocortins include melanocyte-stimulating hormones (MSH) such as α -MSH, β -MSH and γ -MSH, as well as adrenocorticotrophic hormone 20 (ACTH). Individual ligands can bind to multiple MC receptors with differing relative affinities. The variety of ligands and MC receptors with differential tissue-specific expression likely provides the molecular basis for the diverse physiological effects of 25 melanocortins and MC receptors. For example, α -MSH antagonizes the actions of immunological substances such as cytokines and acts to modulate fever, inflammation and immune responses (Catania and Lipton, Annals N. Y. Acad. Sci. 680:412-423 (1993)).

30 The role of certain specific MC receptors in some of the physiological effects described above for MC receptors has been elucidated. For example, MCR-1 is

involved in pain and inflammation. MCR-1 mRNA is expressed in neutrophils (Catania et al., Peptides 17:675-679 (1996)). The anti-inflammatory agent α -MSH was found to inhibit migration of neutrophils. Thus, the 5 presence of MCR-1 in neutrophils correlates with the anti-inflammatory activity of α -MSH.

An interesting link of MC receptors to regulation of food intake and obesity has recently been 10 described. The brain MC receptor MCR-4 has been shown to function in the regulation of body weight and food intake. Mice in which MCR-4 has been knocked out exhibit weight gain (Huszar et al., Cell 88:131-141 (1997)). In addition, injection into brain of synthetic peptides that 15 mimic melanocortins and bind to MCR-4 caused suppressed feeding in normal and mutant obese mice (Fan et al., Nature 385:165-168 (1997)). These results indicate that the brain MC receptor MCR-4 functions in regulating food intake and body weight.

20

Due to the varied physiological activities of MC receptors, high affinity ligands of MC receptors could be used to exploit the varied physiological responses of MC receptors by functioning as potential therapeutic 25 agents or as lead compounds for the development of therapeutic agents. Furthermore, due to the effect of MC receptors on the activity of various cytokines, high affinity MC receptor ligands could also be used to regulate cytokine activity.

30

A variety of assays can be used to identify or characterize MC receptor ligands of the invention. For example, the ability of a 2-aminobenzoxazole derivative

compound to compete for binding of a known MC receptor ligand can be used to assess the affinity and specificity of a 2-aminobenzoxazole derivative compound for one or more MC receptors. Any MC receptor ligand can be used so long as the ligand can be labeled with a detectable moiety. The detectable moiety can be, for example, a radiolabel, fluorescent label or chromophore, or any detectable functional moiety so long as the MC receptor ligand exhibits specific MC receptor binding. A particularly useful detectable MC receptor ligand for identifying and characterizing other MC receptor ligands is ¹²⁵I-HP 467, which has the amino acid sequence Ac-Nle-Gln-His-(p(I)-D-Phe)-Arg-(D-Trp)-Gly-NH₂ and is described in Dooley et al., "Melanocortin Receptor Ligands and Methods of Using Same," U.S. patent application 09/027,108, filed February 20, 1998, which is incorporated herein by reference. HP 467 is a para-iodinated form of HP 228.

Using assay methods such as those described above, binding kinetics and competition with radiolabeled HP 467 can confirm that 2-aminobenzoxazole derivative compounds of the invention bind to one or more MC receptors. Furthermore, 2-aminobenzoxazole derivative compounds of the invention can exhibit a range of affinities and specificity for various MC receptors.

The invention provides MC receptor ligands that can bind to several MC receptors with similar affinity. In addition, the invention also provides MC receptor ligands that can be selective for one or more MC receptors. As used herein, the term "selective" means that the affinity of a MC receptor ligand differs between

one MC receptor and another by about 10-fold, generally about 20- to 50-fold, and particularly about 100-fold. In some cases, a MC receptor ligand having broad specificity is desired. In other cases, it is desirable 5 to use MC receptor ligands having selectivity for a particular MC receptor. For example, MCR-1 ligands are particularly useful for treating pain and inflammation, whereas MCR-4 ligands are useful for treating obesity. The binding characteristics and specificity of a given MC 10 receptor ligand can be selected based on the particular disease or physiological effect that is desired to be altered.

Another assay useful for identifying or 15 characterizing MC receptor ligands measures signaling of MC receptors. MC receptors are G protein-coupled receptors that couple to adenylate cyclase and produce cAMP. Therefore, measuring cAMP production in a cell expressing a MC receptor and treated with a MC receptor 20 ligand can be used to assess the function of the MC receptor ligand in activating a MC receptor.

Ligands for MC-3 that can alter the activity of an MC-3 receptor can be useful for treating sexual 25 dysfunction and other conditions or conditions associated with MC-3 such as inflammation. Other MC-3-associated conditions that can be treated with the MC-3 receptor ligands include disuse deconditioning; organ damage such as organ transplantation or ischemic injury; adverse 30 reactions associated with cancer chemotherapy; diseases such as atherosclerosis that are mediated by free radicals and nitric oxide action; bacterial endotoxic sepsis and related shock; adult respiratory distress

syndrome; and autoimmune or other patho-immunogenic diseases or reactions such as allergic reactions or anaphylaxis, rheumatoid arthritis, inflammatory bowel disease, ulcerative colitis, glomerulonephritis, systemic 5 lupus erythematosus, transplant atherosclerosis and parasitic mediated immune dysfunctions such as Chagas's disease. -

The invention further provides a method for 10 treating an MC-3-associated condition in a subject. The term "MC-3-associated condition" includes any condition or condition mediated by MC-3 or can be affected by binding an MC-3 ligand. Such conditions include inflammation and sexual dysfunction.

15

The term "sexual dysfunction" herein means any condition that inhibits or impairs normal sexual function, including coitus. However, the term need not be limited to physiological conditions, but may include 20 psychogenic conditions or perceived impairment without a formal diagnosis of pathology.

In males, sexual dysfunction includes erectile dysfunction. The term "erectile dysfunction" or 25 "impotence" means herein the inability or impaired ability to attain or sustain an erection that would be of satisfactory rigidity for coitus. Sexual dysfunction in males can also include premature ejaculation and priapism, which is a condition of prolonged and sometimes 30 painful erection unrelated to sexual activity, often associated with sickle-cell disease.

In females, sexual dysfunction includes sexual arousal disorder. The term "sexual arousal disorder" means herein a persistent or recurrent failure to attain or maintain the lubrication-swelling response of sexual 5 excitement until completion of sexual activity. Sexual dysfunction in females can also include inhibited orgasm and dyspareunia, which is painful or difficult coitus. Sexual dysfunction can also be manifested as inhibited sexual desire or inhibited lordosis behavior in animals.

10

In addition, the ability of the compounds to inhibit bacterial growth, and therefore be useful to that infection, can be determined by methods well known in the art. Compounds of the present invention can be shown to 15 have antimicrobial activity by the *in vitro* antimicrobial activity assay described below and, therefore, are useful as antimicrobial agents.

Moreover, an exemplary *in vitro* antimicrobial 20 activity assay is described in Blondelle and Houghten, *Biochemistry* 30:4671-4678 (1991), which is incorporated herein by reference. In brief, *Staphylococcus aureus* ATCC 29213 (Rockville, MD) is grown overnight at 37°C in Mueller-Hinton broth, then re-inoculated and incubated at 25 37°C to reach the exponential phase of bacterial growth (i.e., a final bacterial suspension containing 10^5 to 5×10^5 colony-forming units/ml). The concentration of cells is established by plating 100 µl of the culture solution using serial dilutions (e.g., 10^{-2} , 10^{-3} and 10^{-4}) onto 30 solid agar plates. In 96-well tissue culture plates, compounds, individual or in mixtures, are added to the bacterial suspension at concentrations derived from serial two-fold dilutions ranging from 1500 to 2.9 µg/ml.

The plates are incubated overnight at 37°C and the growth determined at each concentration by OD₆₂₀ nm. The IC₅₀ (the concentration necessary to inhibit 50% of the growth of the bacteria) can then be calculated.

5

The competitive ELISA method which can be used here is a modification of the direct ELISA technique described previously in Appel et al., J. Immunol. 144:976-983 (1990), which is incorporated herein by reference. It differs only in the MAb addition step. Briefly, multi-well microplates are coated with an antigenic peptide at a concentration of 100 pmol/50 µl. After blocking, 25 µl of a 1.0 mg/ml solution of each mixture of a synthetic combinatorial library (or individual compound) is added, followed by MAb 125-10F3 (Appel et al., *supra*) (25 µl per well). The MAb is added at a fixed dilution in which the bicyclic guanidine in solution effectively competes for MAb binding with the antigenic peptide adsorbed to the plate. The remaining steps are the same as for direct ELISA. The concentration of compound necessary to inhibit 50% of the MAb binding to the control peptide on the plate (IC₅₀) is determined by serial dilutions of the compound.

25

Alternative screening can be done with radio-receptor assays. The radio-receptor assay, can be selective for any one of the μ , κ , or δ opiate receptors. Compounds of the present invention can be useful *in vitro* for the diagnosis of relevant opioid receptor subtypes, such as κ , in the brain and other tissue samples. Similarly, the compounds can be used *in vivo* diagnostically to localize opioid receptor subtypes.

The radio-receptor assays are also an indication of the compounds' analgesic properties as described, for example, in Dooley et al., *Proc. Natl. Acad. Sci.*, 90:10811-10815 (1993). For example, it can 5 be envisioned that these compounds can be used for therapeutic purposes to block the peripheral effects of a centrally-acting pain killer. For instance, morphine is a centrally acting pain killer. Morphine, however, has a number of deleterious effects in the periphery which are 10 not required for the desired analgesic effects, such as constipation and pruritus (itching). While it is known that the many compounds do not readily cross the blood-brain barrier and, therefore, elicit no central effect, the subject compounds can have value in blocking the 15 periphery effects of morphine, such as constipation and pruritus. Accordingly, the subject compounds can also be useful as drugs, namely as analgesics, or to treat pathologies associated with other compounds which interact with the opioid receptor system.

20

Additionally, such compounds can be tested in a σ receptor assay. Ligands for the σ receptor can be useful as antipsychotic agents, as described in Abou-Gharia et al., *Annual Reports in Medicinal Chemistry*, 25 28:1-10 (1993).

Radio-receptor assays can be performed with particulate membranes prepared using a modification of the method described in Pasternak et al., *Mol. Pharmacol.* 30 11:340-351 (1975), which is incorporated herein by reference. Rat brains frozen in liquid nitrogen can be obtained from Rockland (Gilbertsville, PA). The brains are thawed, the cerebella removed and the remaining

tissue weighed. Each brain is individually homogenized in 40 ml Tris-HCl buffer (50 mM, pH 7.4, 4°C) and centrifuged (Sorvall® RC5C SA-600: Du Pont, Wilmington, DE) (16,000 rpm) for 10 minutes. The pellets are 5 resuspended in fresh Tris-HCl buffer and incubated at 37°C for 40 minutes. Following incubation, the suspensions are centrifuged as before, the resulting pellets resuspended in 100 volumes of Tris buffer and the suspensions combined. Membrane suspensions are prepared 10 and used in the same day. Protein content of the crude homogenates generally range from 0.15-0.2 mg/ml as determined using the method described in Bradford, M.M., *Anal. Biochem.* 72:248-254 (1976), which is incorporated herein by reference.

15

Binding assays are carried out in polypropylene tubes, each tube containing 0.5 ml of membrane suspension. 8 nM of DAMGO (specific activity = 36 Ci/mmol, 160,000 cpm per tube; which can be obtained from 20 Multiple Peptide Systems, San Diego, CA, through NIDA drug distribution program 271-90-7302) and 80 µg/ml of the subject compound, individual or as a mixture, and Tris-HCl buffer in a total volume of 0.65 ml. Assay tubes are incubated for 60 mins. at 25°C. The reaction 25 is terminated by filtration through GF-B filters on a Tomtec harvester (Orange, CT). The filters are subsequently washed with 6 ml of Tris-HCl buffer, 4°C. Bound radioactivity is counted on a Pharmacia Biotech Betaplate Liquid Scintillation Counter (Piscataway, NJ) 30 and expressed in cpm. To determine inter- and intra-assay variation, standard curves in which ³H-DAMGO is incubated in the presence of a range of concentrations of unlabeled DAMGO (0.13-3900 nM) are generally included in

each plate of each assay (a 96-well format). Competitive inhibition assays are performed as above using serial dilutions of the bicyclic guanidines, individually or in mixtures. IC₅₀ values (the concentration necessary to 5 inhibit 50% of ³H-DAMGO binding) are then calculated. IC₅₀ values of less than 1000 nM are indicative of highly active opioid compounds which bind to the μ receptor, with particularly active compounds having IC₅₀ values of 100 nM or less and the most active compounds with values 10 of less than 10 nM.

As opposed to this μ receptor selective assay, which can be carried out using ³H-DAMGO as radioligand, as described above, assays selective for κ receptors can be 15 carried out using [³H]-U69,593 (3 nM, specific activity 62 Ci/mmol) as radioligand. Assays selective for δ opiate receptors can be carried out using tritiated DSLET ([D-Ser², D-Leu⁵]-threonine-enkephalin) as radioligand. Assays selective for the σ opiate receptor can use 20 radiolabeled pentazocine as ligand.

Screening of combinatorial libraries and compounds of the invention can be done with an anti-fungal assay. Compounds of the present invention 25 can be useful for treating fungal infections.

Screening of combinatorial libraries and compounds of the invention also can be done with a calmodulin-dependent phosphodiesterase (CaMPDE) assay. 30 Compounds of the present invention can be useful as calmodulin antagonists.

Calmodulin (CaM), which is the major intracellular calcium receptor, is involved in many processes that are crucial to cellular viability. In particular, calmodulin is implicated in calcium-stimulated cell proliferation. Calmodulin antagonists are, therefore, useful for treating conditions associated with increased cell proliferation, for example, cancer. In addition, calmodulin antagonists such as compounds of the subject invention are useful both in vitro and in vivo for identifying the role of calmodulin in other biological processes. The disadvantages of known antagonists such as trifluoperazine and N-(4-aminobutyl)-5-chloro-2-naphthalenesulfonamide (W13) include their non-specificity and toxicity. In contrast, advantages of the combinatorial libraries and compounds of the subject invention as calmodulin antagonists include their reduced flexibility and ability to generate broader conformational space of interactive residues as compared to their linear counterparts.

20

An example of an assay that identifies CaM antagonists is a CaMPDE assay. In brief, samples are mixed with 50 μ l of assay buffer (360 mM Tris, 360 mM Imidazole, 45 mM $Mg(CH_3COO)_2$, pH 7.5) and 10 μ l of $CaCl_2$ (4.5 mM) to a final volume of 251 μ l. 25 μ l of calmodulin stock solution (Boehringer Mannheim; 0.01 μ g/ μ l) is then added and the samples then sit at room temperature for 10 minutes. 14 μ l of PDE (Sigma; 2 Units dissolved in 4 ml of water; stock concentration: 0.0005 Units/ μ l) is then added, followed by 50 μ l of 5'-nucleotidase (Sigma; 100 Units dissolved in 10 ml of 10 mM Tris-HCl containing 0.5 mM $Mg(CH_3COO)_2$, pH 7.0; stock concentration: 10 Units/ml). The samples are then

incubated for 10 minutes at 30°C. 50 µl of adenosine 3',5'-cyclic monophosphate (cAMP) (20 mM in water at pH 7.0) is added, the samples incubated for 1 hour at 30°C and then vortexed. 200 µl of trichloroacetic acid (TCA) 5 (55% in water) is added to a 200 µl sample aliquot, which is then vortexed and centrifuged for 10 minutes. 80 µl of the resulting supernatants of each sample is transferred to a 96-well plate, with 2 wells each containing 80 µl of each sample. 80 µl of ammonium 10 molybdate (1.1% in 1.1N H₂SO₄) is then added to all the wells, and the OD of each were determined at 730nm, with the values later subtracted to the final OD reading. 16 µl of reducing agent (6g sodium bisulfite, 0.6g sodium sulfite and 125mg of 1-amino-2-naphtol-4-sulfonic acid in 15 50ml of water) is then added to one of each sample duplicate and 16 µl of water is added to the other duplicate. After sitting for 1 hour at room temperature, the OD of each well is determined at 730nm. The percent inhibition of calmodulin activity is then calculated for 20 each sample, using as 0% inhibition a control sample containing all reagents without any test samples and as 100% inhibition a control sample containing test samples and all reagents except calmodulin. In addition, the percent inhibition of phosphodiesterase activity was 25 determined by following a similar protocol as the CaMPDE assay described above, except not adding calmodulin to the sample mixture and calculating the percent inhibition by using as 0% inhibition a control reagent without any test samples and as 100% inhibition a control sample 30 containing test samples and all reagents except cAMP.

The following examples are provided to illustrate but not limit the present invention. The following abbreviations have the corresponding meanings:

5 MBHA : 4-methylbenzhydrylamine;
DMF : N,N-dimethylformamide;
HOEt : 1-hydroxybenzotriazole;
DMSO : dimethylsulfoxide;
Boc : tert-butoxycarbonyl;
10 FMOC : 9-fluorenyl-methoxycarbonyl;
DMAP : 4-dimethylamino-pyridine;
DIC : N,N'-diisopropylcarbodiimide;
TFA : trifluoroacetic acid;
DIEA : N,N-diisopropylethylamine;
15 DCM : dichloromethane;
TMOF: trimethylorthoformate;
HATU : azabenzotriazolyl-N,N,N',N'-tetramethyluronium hexafluorophosphate;
CDI : carbonyldiimidazole
20 NMP : N-methylpyrrolidinone
DMA : N,N-dimethyl acetamide
RT : room temperature
IPA : isopropyl alcohol
MeOH: methanol
25 MeOEtOH : 2-methoxyethanol
DCE : 1,2-dichloroethane
THF : tetrahydrofuran
ACN : acetonitrile
Wang resin : *p*-benzyloxybenzyl alcohol-polystyrene
30 Br-Wang resin : *p*-benzyloxybenzyl bromide-polystyrene
PP : polypropylene
PPh₃Br₂ : triphenylphosphine dibromide
DMAP : 4-dimethylamino-pyridine

KOtBu : potassium tert-butoxide
NaOMe : sodium methoxide
BtCH2CN : 1-(cyanomethyl)benzotriazole
DBU : 1,8-diazabicyclo[5.4.0]undec-7-ene
5 Boc : tertbutoxycarbonyl;
AcOH : acetic acid
HPLC/MS : high performance liquid chromatography - mass spectrometry;
FIA/MS : flow injection analysis - mass spectrometry
10 ELSD : evaporative light scattering detector
THB : Todd Hewitt Broth
OD : optical density

Example 1

15

Synthesis of a combinatorial library of 2-amino benzoxazole derivatives (where Z is formula A)

Step 1. Preparation of SASRIN Aldehyde Resin

20

Five 2L bottles were run in parallel to prepare 1kg of SASRIN aldehyde resin. The following description is for one of the five identical reactions.

25

A 2L Pyrex media bottle was charged with 200 g Merrifield resin (100-200 mesh, 1.46 mmol/g). DMF (700 mL) was added and the bottle was shaken by hand to distribute the solvent within the swollen resin. A 1L Pyrex media bottle was charged with 4-hydroxy-2-30 methoxybenzaldehyde (140 g, 0.92 mol) and the aldehyde was dissolved in DMF (600mL). The aldehyde solution was cooled to 0° C (ice bath) and potassium tert-butoxide (98 g, 0.88 mol) was added in two equal portions waiting about 5 min. between additions. The bottle was removed

from the ice bath and shaken periodically to help dissolve the potassium tert-butoxide. After the second portion of potassium tert-butoxide was added, the bottle is allowed to warm to 25°C. After 30 min. at 25°C, the 5 potassium tert-butoxide dissolved, giving the solution a dark amber color.

The phenoxide solution was added to the swollen resin in four portions, shaking between portions. The 2L 10 bottles were clamped horizontally in an orbital shaker oven and allowed to shake at 25°C for 30 min. The temperature was then increased to 50° C and the reaction shaken for 14 h. After cooling, the resin slurry was poured into a 10" x 12" 3-sided porous polypropylene 15 packet (tea bag) sitting in a 2L beaker. After the solvent mixture had drained from the resin, the fourth side of the tea bag was sealed and the tea bags were washed in wide-mouth HDPE Nalgene bottles as follows: 2 x DMF, 4 x DMF/H₂O (4:1), 4 x DMF, 4 x MeOH. The tea bags 20 were allowed to air dry in a fume hood. From 200 g of starting Merrifield resin, 238 g of SASRIN aldehyde resin was obtained with a loading of 1.2 mmol/g.

Step 2. Reductive Amination of SASRIN Aldehyde Resin with 25 Primary Amines (Step 1 of Figure 1)

SASRIN aldehyde resin was swollen in 1% AcOH/DMF (by volume). The amine (0.15M) was added and the bottle(s) placed on a shaker for 30 min. NaBH₃CN (2 30 eq to amine, 0.3M) was added, and the reaction bottles placed on a shaker at room temperature for 18 h. The resin was washed as follows: DMF (4x), MeOH (4x) and then .

allowed to air dry. For the amines that were hydrochloride salts, 1 eq of DIEA was added. The amines added were as follows:

- 5 CYCLOPROPYLAMINE
- CYCLOPENTYLAMINE
- CYCLOHEXYLAMINE
- AMINOMETHYLCYCLOHEXANE
- L-LEUCINE
- 10 1-(2-AMINOETHYL) PYRROLIDINE
- 1-(3-AMINOPROPYL)-2-PYRROLIDINONE
- 1-(1-NAPHTHYL) ETHYLAMINE
- 1-NAPHTHALENEMETHYLAMINE
- CYCLOHEPTYLAMINE
- 15 TETRAHYDROFURFURLYLAMINE
- 2-THIOPHENEMETHYLAMINE
- 3, 4-METHYLENEDIOXYBENZYLAMINE
- 4-AMINO-2, 2, 6, 6-TETRAMETHYLPIPERIDINE
- 4-(2-AMINOETHYL) MORPHOLINE
- 20 N-(3-AMINOPROPYL) MORPHOLINE
- 2-(2-AMINOETHYL) PYRIDINE
- 3-(AMINOMETHYL) PYRIDINE
- ETHYL 4-AMINO-1-PIPERIDINECARBOXYLATE
- 4-AMINO-1-BENZYLPIPERIDINE
- 25 1-(2-AMINOETHYL) PIPERIDINE
- P-ANISIDINE
- 1, 3-DIMETHYLBUTYLAMINE
- 1-METHYL-3-PHENYLPROPYLAMINE
- 2-AMINO-5-DIETHYLAMINOPENTANE
- 30 BENZYLAMINE
- 2-FLUOROBENZYLAMINE
- 2-CHLOROBENZYLAMINE
- 3-FLUOROBENZYLAMINE
- 3, 4-DICHLOROBENZYLAMINE
- 35 3-METHOXYBENZYLAMINE
- 3, 4-DIMETHOXYBENZYLAMINE
- 3-(TRIFLUOROMETHYL) BENZYLAMINE
- 4-FLUOROBENZYLAMINE
- 4-METHYLBENZYLAMINE
- 40 N, N-DIETHYLETHYLENEDIAMINE
- 2-METHOXYETHYLAMINE
- 2-(3, 4-DIMETHOXYPHENYL) ETHYLAMINE
- 2-(4-CHLOROPHENYL) ETHYLAMINE
- 2-(4-METHOXYPHENYL) ETHYLAMINE
- 45 PROPARGYLAMINE
- ALLYLAMINE
- N, N-DIMETHYL-1, 3-PROPANEDIAMINE

N, N-DIETHYL-1, 3-PROPANEDIAMINE
1-(3-AMINOPROPYL) IMIDAZOLE
2-(TRIFLUOROMETHYL) BENZYLAMINE
ETHYL 4-AMINOBUTYRATE HYDROCHLORIDE
5 4-TERT-BUTYL CYCLOHEXYLAMINE
1-(3-AMINOPROPYL) PYRROLIDINE
2-BROMOBENZYLAMINE
2, 4-DIMETHYL BENZYLAMINE
N-(2-AMINOETHYL) -N-ETHYL-M-TOLUIDINE
10 2-ETHOXYETHYLAMINE
3-CHLOROBENZYLAMINE
3-(METHYLTHIO) PROPYLAMINE
(R) - (-) -1-CYCLOHEXYLETHYLAMINE
THIOPHENE-2-ETHYLAMINE
15 3, 5-DIMETHOXYBENZYLAMINE
2, 4-DICHLOROPHENETHYLAMINE
4-(TRIFLUOROMETHOXY) BENZYLAMINE
L-PHENYLALANINE
L-ALANINE
20 2-FLUOROPHENETHYLAMINE
2-(4-FLUOROPHENYL) ETHYLAMINE
N-(3-AMINOPROPYL) -N-METHYLANILINE
L-ARGININE

25

Step 3. Coupling of Thiomethylbenzoxazole Cores to Resin Bound Secondary Amines (Step 2 of Figure 1).

(a) Boc-Deprotection for Boc-Arg (Tos)-mBHA containing
30 bags (see starting material shown in Figure 2): Bags were rinsed with DCM, treated with a solution of 55% TFA/DCM for 30 minutes, then washed as follows: DCM, IPA (2x), DCM (2x), MeOH, and then air dried. Just prior to acylation did neutralization as follows: DCM, 35 5% DIEA/DCM, DCM.

(b) Acylation of all bags was carried out in two batches, each done in a 20L Nalgene container, with both Sasrin and mBHA resins reacted together. For example, a batch of 364 bags (0.66 mol) was placed in 40 the 20L Nalgene bottle, a solution of DCM/DMF (ratio 2:1, 9.5L) was added followed by 5-carboxy-2-

(methylthio)-1,3-benzoxazole (0.2M, 1.97 mol, 410.8 g), 4-dimethylaminopyridine (DMAP, 1.31 mol, 160.09 g), and 1,3-diisopropylcarbodiimide (DIC, 1.97 mol, 308 ml). The bottle was shaken, then vented one time. The 5 bottle was then shaken for 18 h at room temperature. The resin was washed as follows: DMF (6x), MeOH (4x). The bags were then air dried.

Step 4. Displacement of S-Me by Symmetrical Diamines
10 (Step 3 of Figure 1).

Eight diamines were used:

PIPERAZINE
15 4,4'-BIPIPERIDINE DIHYDROCHLORIDE
1,4-BIS(3-AMINOPROPYL)PIPERAZINE
HOMOPIPERAZINE
1,4-DIAMINOBUTANE
N,N'-DIETHYL-1,3-PROPANEDIAMINE
20 1,3-DI-4-PIPERIDYLPROPANE
1,8-DIAMINO-3,6-DIOXAOCTANE

The reactions were run in wide-mouthed glass containers ranging from 1L to 5L in size. The excess 25 ranged from 18 to 50 fold, depending on the amount of solvent necessary to adequately cover the bags. Bags were added to the appropriate container, anhydrous DMSO was added, and then the diamine (0.6M). Containers were placed in an oven shaker and heated at 75°C for 90 h. The 30 containers were then removed from the oven and allowed to cool.

One DMF wash was performed per container, then the bags were combined in a 20L Nalgene container for the 35 remaining washes: DMF (5x), MeOH (4x), then bags were placed in a fume hood to air dry.

Step 5. Derivatization of the Substituted Aminobenzoxazole (Step 4 of Figure 1).

5 **Acylation (X=C(O)):** For 45 μ mol aminobenzoxazole resin per well of a 96-well microtiter plate, 700 μ L RCO₂H/DIEA/DMAP/DCM-DMF (0.5M, 0.35 mmol RCO₂H; 1.1M, 0.77 mmol DIEA; 0.16M, 0.112 mmol DMAP; 2:1 DCM-DMF) and 700 μ L HBTU/DMF (0.5M, 0.35mmol) were added to each well.

10 The carboxylic acids (RCO₂H) used were as follows:

CYCLOPROPANE CARBOXYLIC ACID
1-METHYL CYCLOPROPANE-1-CARBOXYLIC ACID
1-METHYL-1-CYCLOHEXANE CARBOXYLIC ACID
15 TRANS-1,2-CYCLOHEXANE DICARBOXYLIC ACID
(-)-MENTHOXYACETIC ACID
1,1-CYCLOHEXANE DIACETIC ACID
BENZOIC ACID
N-PHENYLANTHRANILIC ACID
20 FLUFENAMIC ACID
2,4-DIMETHYL BENZOIC ACID
3-BENZOYL BENZOIC ACID
2-PROPYLPENTANOIC ACID
2-ETHYLHEXANOIC ACID
25 TRANS-2-PENTENOIC ACID
TERT-BUTYLACETIC ACID
2-KETOBUTYRIC ACID
2-ETHYL-2-HYDROXYBUTYRIC ACID
METHOXYACETIC ACID
30 2-(TRIFLUOROMETHYL) PHENYLACETIC ACID
4-(TRIFLUOROMETHYL) PHENYLACETIC ACID
5-CHLOROVALERIC ACID
3-FUROIC ACID
N-ACETYL-DL-TRYPTOPHAN
35 3-INDOLEPROPIONIC ACID
3,4-DIFLUOROPHENYLACETIC ACID
3-(PHENYLSULFONYL) PROPIONIC ACID
2,4-DIFLUOROBENZOIC ACID
3-CYCLOHEXENE CARBOXYLIC ACID
40 2-BENZOLOXYPHENYLACETIC ACID
N-ACETYL-L-PROLINE
1-ACETYLPIPERIDINE-4-CARBOXYLIC ACID
5-CHLOROTHIOPHENE-2-CARBOXYLIC ACID
2-(2-METHOXYETHOXY) ACETIC ACID
45 BENZO[B]THIOPHENE-3-ACETIC ACID

METHANESULFONYLACETIC ACID
5-HEXYNOIC ACID
3-FLUORO-2-METHYL-BENZOIC ACID
2-METHYL-3-FUROIC ACID
5 6-HEPTYNOIC ACID
5-METHYLISSOXAZOLE-4-CARBOXYLIC ACID

The Plates were capped, vortexed, and placed on a shaker at room temperature for 48 h. The resin was washed by 10 DMF (7x), MeOH (6x), and dried.

Sulfonylation (X=SO₂): For 45 μ mol of aminobenzoxazole resin in each well of a 96-well microtiter plate, 1 mL RSO₂Cl/THF-ACN /NMM/NMI (0.3M, 0.3 15 mmol RSO₂Cl; 20% THF-ACN (by volume); 0.6M, 0.6 mmol NMM; 0.1M, 0.1 mmol NMI) was added to each well. The sulfonyl chlorides (RSO₂Cl) used were as follows:

20 1-NAPHTHALENESULFONYL CHLORIDE
2-NAPHTHALENESULFONYL CHLORIDE
2-ACETAMIDO-4-METHYL-5-THIAZOLESULFONYL CHLORIDE
2-THIOPHENESULFONYL CHLORIDE
8-QUINOLINESULFONYL CHLORIDE
2-MESITYLENESULFONYL CHLORIDE
25 3-NITROBENZENESULFONYL CHLORIDE
4-BROMOBENZENESULFONYL CHLORIDE
4-FLUOROBENZENESULFONYL CHLORIDE
4-CHLOROBENZENESULFONYL CHLORIDE
4-ACETAMIDOBENZENESULFONYL CHLORIDE
30 4-NITROBENZENESULFONYL CHLORIDE
4-TERT-BUTYLBENZENESULFONYL CHLORIDE
PENTAMETHYLBENZENESULFONYL CHLORIDE
2,3,5,6-TETRAMETHYLBENZENESULFONYL CHLORIDE
P-XYLENE-2-SULFONYL CHLORIDE
35 3,4-DICHLOROBENZENESULFONYL CHLORIDE
3-CHLORO-4-FLUOROBENZENESULPHONYL CHLORIDE
4-ETHYLBENZENESULFONYL CHLORIDE
4-N-PROPYLBENZENESULFONYL CHLORIDE
4-N-AMYLBENZENESULFONYL CHLORIDE
40 4-ISOPROPYLBENZENESULPHONYL CHLORIDE
3-FLUOROBENZENESULPHONYL CHLORIDE
4-(TRIFLUOROMETHYL)BENZENESULFONYL CHLORIDE
2-CHLOROBENZENESULFONYL CHLORIDE

5-CHLOROTHIOPHENE-2-SULFONYL CHLORIDE
3-CHLOROBENZENESULFONYL CHLORIDE
3,5-DICHLOROBENZENESULFONYL CHLORIDE
M-TOLUENESULFONYL CHLORIDE
5 2-CHLORO-6-METHYLBENZENESULFONYL CHLORIDE
2-BROMOBENZENESULFONYL CHLORIDE
2,4-DICHLOROBENZENESULFONYL CHLORIDE
1-METHYLLIMIDAZOLE-4-SULPHONYL CHLORIDE
2-(METHOXCARBONYL)THIOPHENE-3-SULPHONYL CHLORIDE
10 P-STYRENESULFONYL CHLORIDE
3,4-DIFLUOROBENZENESULPHONYL CHLORIDE
4-PENTYLBENZENE-1-SULFONYL CHLORIDE
4-N-BUTYLBENZENESULFONYL CHLORIDE
3-CHLORO-4-METHYLBENZENESULPHONYL CHLORIDE
15 2-METHYLSULFONYLBENZENESULFONYL CHLORIDE

Plates were capped, vortexed, and placed on a shaker at room temperature for 48 h. The resin was washed by ACN (6x), MeOH (6x), and then air dried.

20

Step 6. Cleavage from Linker and Extraction (Step 5 of Figure 5).

Because three different types of resins were 25 used, three different cleavage procedure resulted.

(a) *Sasrin resin, no side-chain protection in the R_1 position:* To the dry microtiter plates containing the aminobenzoxazole resins was added 0.5 mL of 10% TFA/DCM 30 to each well containing resin. Plates were capped and placed on a shaker at room temperature for 3 h. Plates were transferred to a GENEVAC to remove the volatile TFA/DCM solution. The plates were extracted with acetic acid and the extractions were lyophilized. 35 The final substituted-aminobenzoxazole products were then analyzed by FIA/MS and HPLC/ELSD.

(b) *Sasrin resin, tert-Butyl ester protection of the R_1 side-chain:* To the dry microtiter plates containing the

aminobenzoxazole resins was added 0.5 mL of 20% TFA/DCM to each well containing resin. Plates were capped and placed on a shaker at room temperature for 3 h. Plates were transferred to a GENEVAC (Valley College, New York) to remove the volatile TFA/DCM solution. The plates were extracted with acetic acid and the extractions were lyophilized. The final substituted-aminobenzoxazole products were then analyzed by FIA/MS and HPLC/ELSD.

10 (c) *MBHA resin*: The dry microtiter plates containing the aminobenzoxazole resin were placed in an HF chamber and sealed. The chamber was flushed with nitrogen for 1 h. Gaseous HF was then added to the chamber for 30 minutes. The chamber was isolated and allowed to stand 15 at room temperature for 2 h. To remove HF, the chamber was flushed with nitrogen for 2.5 h. The plates were removed from the HF chamber and placed in a dessicator under vacuum overnight. The plates were extracted with acetic acid and the extractions were lyophilized. The 20 final substituted-aminobenzoxazole products were then analyzed by FIA/MS and HPLC/ELSD.

Example 2

25 **Synthesis of a combinatorial library of 2-amino benzoxazole derivatives (where Z is formula B)**

30 **Step 1. Reductive Amination of SASRIN Aldehyde Resin with Primary Amines**

2.5 g tea bags containing SASRIN aldehyde resin were swollen in 1% AcOH/DMF (by volume). An amine (0.15M) was added and the bottle(s) placed on a shaker 35 for 30 min. (see amines listed in step 1 of Example 1).

NaBH₃CN (2 eq to amine, 0.3M) was added and the reaction bottles placed on a shaker at room temperature for 18 hours, with the bottles need to be vented after the first 30 min. to prevent pressure build up due to the release 5 of H_{2(g)}. The resin was washed as follows: DMF (4x), MeOH (4x) and then allowed to air dry. For the amines that were hydrochloride salts, 1 eq of DIEA was added.

Step 2. Coupling of Thiomethylbenzoxazole Cores to Resin
10 Bound Secondary Amine

Acylation of all bags was carried out in two batches, each done in a 20L Nalgene container. For example, a batch of 256 bags was placed in the 20L 15 Nalgene bottle, a solution of DCM/DMF (ratio 2:1, 7L) was added followed by 5-carboxy-2-(methylthio)-1,3-benzoxazole (0.2M, 1.4 mol, 293 g), 4-dimethylaminopyridine (DMAP, 0.91 mol, 111 g), and 1,3-diisopropylcarbodiimide (DIC, 1.4 mol, 220 ml). The 20 container was shaken, vented and placed on a shaker for 18 h at room temperature. The resin was washed as follows: DMF (6x), MeOH (4x). The bags were dried.

Step 3. Displacement of S-Me by Amino Alcohols
25

3 amino alcohols used: L-pyrrolinol, 3-piperidine methanol, and N-(2-hydroxyethyl)piperazine. The reactions were run in wide-mouthed glass containers ranging from 4L to 6L in size. Bags were added to the 30 appropriate container, N,N-dimethylacetamide was added followed by tetramethylguanidine (TMG) and the amino alcohol (0.6M). Containers were placed in an oven shaker and heated at 73° C for 64 h. The containers were then removed from the oven and allowed to cool. One DMF wash

was performed per container, then the bags were combined in a 20L Nalgene container for the remaining washes: DMF (5x), MeOH (4x). The bags were placed in a fume hood to air dry.

5

Step 4. Bromination of the Primary Alcohols

Bromination was carried out in four batches. The following description is for one of the four 10 identical batches. A 8 L glass vessel wash charged with 7 L of DCM, $\text{Ph}_3\text{P Br}_2$ (840 g, 2.0 mol) and Et_3N (840 mL, 6.0 mol). After mixing the solution to dissolve the reagent, 130 tea bags were added and the vessel placed on a shaker for 16 h. The bags were washed with DCM (x2), 15 MeOH (x1), DMF (x4), and MeOH (x3). After drying the resin, the intermediates were analyzed by HPLC-MS.

Step 5. Displacement of Bromide with Primary and Secondary Amines

20

After resin distribution into 96 well mircotiter plates, each amine was dissolved in a solution of 0.3M TMG in DMF to make a solution that was 0.6M in amine. The amines used were as follows:

25

Nipecotamide
L-Prolinamide
Pyrrolidine
Piperidine
30 1-methylpiperazine
Ethanolamine
Morpholine
2-piperidinemethanol
N-methylbenzylamine
35 Ethyl isonipecotate
1-phenylpiperazine
1-(2-pyrimidyl)-piperazine

N-methylcyclohexylamine
N-methylisobutylamine
Thiomorpholine
R-(-)-1-cyclohexylethylamine
5 1,2,3,4,-tetrahydroisoquinoline
N-ethylbenzylamine
N,N,N'-triethylmethylenediamine
1-benzylpiperazine
Neopentylamine
10 Aminomethylcyclohexane
Homopiperazine
Decahydroquinoline
Hexamethyleneimine
Ethyl nipecotate
15 N-methyl-N-propylamine
N,N,N'-trimethyl-1,3-propanediamine
4-hydroxypiperidine
2,6-dimethylpiperazine
1-methylhomopiperazine
20 2-methylpiperidine
3,5-dimethylpiperidine
3-(dimethylamino)pyrrolidine
3-(tert-butoxycarbonylamo)pyrrolidine
N-methylallylamine
25 N-methyl-Beta-alanenitrile
Di-(2-picollyl)amine
N-heptylmethylamine
2-(ethylamino)ethanol
N-ethyl-N-butylamine
30 N-ethylpiperazine
2,6-dimethylmorpholine
N-sec-butyl-N-propylamine
N-(N-butyl)-N-propylamine
3-(ethylamino)-propionitrile
35
40 Using robotic delivery, 1 mL of the amine solution was added to the wells of the microtiter plates containing the bromide resins. The plates were vortexed and were placed in a shaker oven at 50° C for 64 h. After cooling to room temperature, the resin was robotically washed using DMF (x8) and MeOH (x6).

Step 6. Cleavage from Linker and Extraction

To dry microtiter plates containing the aminobenzoxazole resins was added 0.5 mL of 10% TFA/DCM to each well. The plates were capped and placed on a shaker at room temperature for 3 h. The plates were transferred to a GENEVAC to remove the volatile TFA/DCM solution. The plates were extracted with AcOH and the extract frozen and lyophilized to afford the products as yellow oils. All of the final products were analyzed by HPLC/MS using ELSD detection to determine purity.

Example 3

15 Anti-microbial Screen

Streptococcus pyogenes (ATCC# 97-03 14289) are grown in Todd Hewitt Broth (THB) (Difco Laboratories #0492-17-6) overnight until they reach an optical density of (OD = 0.636@ 570 nm) by reading 0.1 ml in a 96 well microtiter plate in a Molecular Devices Thermomax. This preparation is kept frozen as stocks in 30% v/v glycerol in 1.5 ml aliquots at -70°C until use. Prior to experiments, 1.5 ml aliquots are thawed and diluted into 50 ml THB. 200 ul of this dilution is added to 92 wells of microtiter plate. To three wells THB (200 ul) is added to serve as a blank and a sterility control. Test compounds in DMSO and appropriate concentrations of DMSO are added to Growth/Solvent Controls at 0 time. Plates are read at 0 time at 570 nm in the Molecular Devices plate reader to obtain compounds correction factors for insoluble or colored compounds. Plates are read again at 4 hrs.

Percent inhibition is calculated with the following formulae:

5 Color correct =

(O.D. 0 hr - Blank 0 hr)-(Solvent Control 0hr - Blank 0 hr) -

% Inhibition =

10 $100 - \frac{\text{O.D. test compound 4 hr} - \text{Blank 4 hr} - \text{color correct}}{\text{O.D. growth/solvent control 4 hr} - \text{Blank 4 hr}}$

EXAMPLE 4

15 Melanocortin Receptor Assay

This example describes methods for assaying binding to MC receptors.

20 All cell culture media and reagents are obtained from GibcoBRL (Gaithersburg MD), except for COSMIC CALF SERUM (HyClone; Logan UT). HEK 293 cell lines are transfected with the human MC receptors hMCR-1, hMCR-3, and hMCR-4 (Gantz et al., Biochem. Biophys. Res. Comm. 200:1214-1220 (1994); Gantz et al., J. Biol. Chem. 268:8246-8250 (1993); Gantz et al. J. Biol. Chem. 268:15174-15179 (1993); Haskell-Leuvano et al., Biochem. Biophys. Res. Comm. 204:1137-1142 (1994); each of which is incorporated herein by reference). Vectors for 30 construction of an hMCR-5 expressing cell line are obtained, and a line of HEK 293 cells expressing hMCR-5 is constructed (Gantz, *supra*, 1994). hMCR-5 has been described previously (Franberg et al., Biochem. Biophys.

Res. Commun. 236:489-492 (1997); Chowdhary et al.,
Cytogenet. Cell Genet. 68:1-2 (1995); Chowdhary et al.,
Cytogenet. Cell Genet. 68:79-81 (1995), each of which is
incorporated herein by reference). HEK 293 cells are
5 maintained in DMEM, 25 mM HEPES, 2 mM glutamine,
non-essential amino acids, vitamins, sodium pyruvate,
10% COSMIC CALF SERUM, 100 units/ml penicillin, 100 µg/ml
streptomycin and 0.2 mg/ml G418 to maintain selection.

10 Before assaying, cells are washed once with
phosphate buffered saline ("PBS"; without Ca^{2+} and Mg^{2+}),
and stripped from the flasks using 0.25% trypsin and
0.5 mM EDTA. Cells are suspended in PBS, 10% COSMIC CALF
SERUM and 1 mM CaCl_2 . Cell suspensions are prepared at a
15 density of 2×10^4 cells/ml for HEK 293 cells expressing
hMCR-3, hMCR-4 or hMCR-5, and 1×10^5 cells/ml for HEK 293
cells expressing hMCR-1. Suspensions are placed in a
water bath and allowed to warm to 37°C for 1 hr.

20 Binding assays are performed in a total volume
of 250 µl for HEK 293 cells. Control and test compounds
are dissolved in distilled water. ^{125}I -HP 467
(50,000 dpm) (2000 Ci/mmol) (custom labeled by Amersham;
Arlington Heights IL) is prepared in 50 mM Tris, pH 7.4,
25 2 mg/ml BSA, 10 mM CaCl_2 , 5 mM MgCl_2 , 2 mM EDTA and added
to each tube. To each tube is added 4×10^3 HEK 293 cells
expressing hMCR-3, hMCR-4 or hMCR-5, or 2×10^4 cells
expressing hMCR-1. Assays are incubated for 2.5 hr at
37°C.

30 GF/B filter plates are prepared by soaking for
at least one hour in 5 mg/ml BSA and 10 mM CaCl_2 . Assays
are filtered using a Brandel 96-well cell harvester

(Brandel Inc.; Gaithersburg, MD). The filters are washed four times with cold 50 mM Tris, pH 7.4, and the filter plates dehydrated for 2 hr and 35 μ l of MICROSCINT is added to each well. Filter plates are counted using a 5 Packard Topcount (Packard Instrument Co.) and data analyzed using GraphPad PRISM v2.0 (GraphPad Software Inc.; San Diego CA) and Microsoft EXCEL v5.0a (Microsoft Corp.; Redmond WA).

10 To assay 2-aminobenzoxazole derivative compounds, binding assays are performed in duplicate in a 96 well format. HP 467 is prepared in 50 mM Tris, pH 7.4, and 125 I-HP 467 is diluted to give 100,000 dpm per 50 μ l. A 2-aminobenzoxazole derivative compound, 15 synthesized as described in Examples 1 to 3, is added to the well in 25 μ l aliquots. A 25 μ l aliquot of 125 I-HP 467 is added to each well. A 0.2 ml aliquot of suspended cells is added to each well to give the cell numbers indicate above, and the cells are incubated at 37°C for 20 2.5 hr. Cells are harvested on GF/B filter plates as described above and counted.

EXAMPLE 5

25 Penile erection due to administration of a 2-aminobenzoxazole derivative compound

Adult male rats are housed 2-3 per cage and are acclimated to the standard vivarium light cycle (12 hr. 30 light, 12 hr. dark), rat chow and water for a least a week prior to testing. All experiments are performed between 9 a.m. and noon and rats are placed in cylindrical, clear plexiglass chambers during the 60

minute observation period. Mirrors are positioned below and to the sides of the chambers, to improve viewing.

Observations begin 10 minutes after an
5 unstraperitoneal injection of either saline or compound. An observer counts the number of grooming motions, stretches, yawns and penile erections (spontaneously occurring, not elicited by genital grooming) and records them every 5 minutes, for a total of 60 minutes. The
10 observer is unaware of the treatment and animals are tested once, with n=6 in each group. Values in the figures represent the group mean and standard error of the mean. HP 228 can be used as a positive control for penile erections. Significant differences between groups
15 are determined by an overall analysis of variance and the Student Neunmann-Keuls post hoc test can be used to identify individual differences between groups (p \leq 0.05).

20 All references cited herein are fully incorporated by reference.

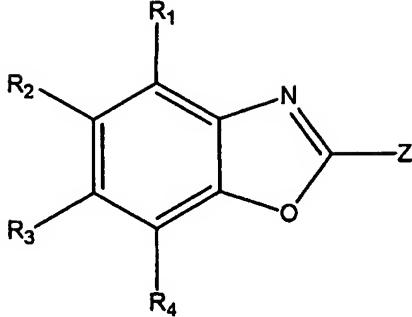
Although the invention has been described with reference to the examples provided above, it should be
25 understood that various modifications can be made by those skilled in the art without departing from the invention. Accordingly, the invention is set out in the following claims.

100

WE CLAIM:

1. A single compound of the structure:

5



10 wherein R₁ and R₄, and one of R₂ and R₃, are independently selected from the group consisting of a hydrogen atom, halo, hydroxy, protected hydroxy, cyano, C₁ to C₁₂ alkyl, C₂ to C₁₂ alkenyl, C₂ to C₁₂ alkynyl, C₁ to C₁₂ substituted alkyl, C₂ to C₁₂ substituted alkenyl, C₂ to C₁₂ substituted alkynyl, C₁ to C₁₂ alkoxy, C₁ to C₁₂ substituted alkoxy, C₁ to C₁₂ acyloxy, C₁ to C₁₂ acyl, C₃ to C₇ cycloalkyl, C₃ to C₇ substituted cycloalkyl, C₅ to C₇ cycloalkenyl, C₅ to C₇ substituted cycloalkenyl, heterocyclic ring, substituted heterocyclic ring, C₇ to C₁₈ phenylalkyl, C₇ to C₁₈ substituted phenylalkyl, C₁ to C₁₂ heterocycloalkyl, C₁ to C₁₂ substituted heterocycloalkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, cyclic C₂ to C₇ alkylene, substituted cyclic C₂ to C₇ alkylene, cyclic C₂ to C₇ heteroalkylene, substituted cyclic C₂ to C₇ heteroalkylene, carboxy, protected carboxy, hydroxymethyl, protected hydroxymethyl, protected amino, protected (monosubstituted) amino, (disubstituted) amino, C₁ to C₁₀

15

20

25

alkyl protected amino, C_1 to C_{10} alkyl protected (monosubstituted) amino, C_1 to C_{10} alkyl(disubstituted) amino, C_1 to C_{10} substituted alkylamino, C_1 to C_{10} substituted alkyl protected (monosubstituted) amino, C_1 to C_{10} substituted alkyl(disubstituted) amino, carboxamide, C_1 to C_{10} alkylthio, C_1 to C_{10} substituted alkylthio, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{10} alkylsulfoxide, C_1 to C_{10} substituted alkylsulfoxide, phenylthio, substituted phenylthio, phenylsulfoxide, substituted phenylsulfoxide, phenylsulfonyl, substituted phenylsulfonyl and the group consisting of (i) the formula $-C(O)NR^{11}R^{12}$, (ii) the formula $-SR^{11}$, (iii) the formula $-OR^{11}$ and (iv) the formula $-C(O)OR^{11}$, wherein R^{11} and R^{12} are, independently, selected from the group consisting of a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} substituted alkenyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocycloalkyl, C_1 to C_{12} substituted heterocycloalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted heterocycle;

the other of R_2 and R_3 is selected from the group consisting of a hydrogen atom, halo, hydroxy, protected hydroxy, carboxy, thio, C_1 to C_{12} alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} alkynyl, C_1 to C_{12} substituted alkynyl, C_2 to C_{12} substituted alkenyl, C_2 to C_{12} substituted alkynyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkoxy, C_1 to C_{12} acyloxy, C_1 to C_{12} acyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, heterocyclic ring, substituted heterocyclic ring, C_7 to C_{18}

phenylalkyl, C₇ to C₁₈ substituted phenylalkyl, C₁ to C₁₂ heterocycloalkyl, C₁ to C₁₂ substituted heterocycloalkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, cyclic C₂ to C₇ alkylene, substituted cyclic C₂ to C₇

5 alkylene, cyclic C₂ to C₇ heteroalkylene, substituted cyclic C₂ to C₇ heteroalkylene, carboxy, protected carboxy, hydroxymethyl, protected hydroxymethyl, protected amino, protected (monosubstituted) amino, (disubstituted) amino, C₁ to C₁₀ alkyl protected amino, C₁ to C₁₀ alkyl protected

10 (monosubstituted) amino, C₁ to C₁₀ alkyl(disubstituted) amino, C₁ to C₁₀ substituted alkyl protected amino, C₁ to C₁₀ substituted alkyl protected (monosubstituted) amino, C₁ to C₁₀ substituted alkyl(disubstituted) amino, carboxamide, C₁ to C₁₀ alkylthio, C₁ to C₁₀ substituted alkylthio, C₁ to C₁₀

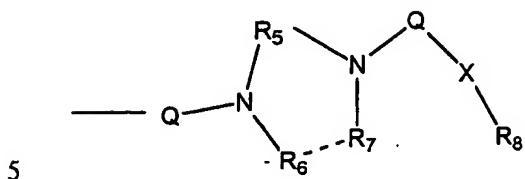
15 alkylsulfonyl, C₁ to C₁₀ substituted alkylsulfonyl, C₁ to C₁₀ alkylsulfoxide, C₁ to C₁₀ substituted alkylsulfoxide, phenylthio, substituted phenylthio, phenylsulfoxide, substituted phenylsulfoxide, phenylsulfonyl, substituted phenylsulfonyl and the group consisting of (i) the formula

20 -C(O)NR¹¹R¹², (ii) the formula -SR¹¹, (iii) the formula -OR¹¹, (iv) the formula -C(O)OR¹¹ and (v) the formula S(O)₂NR¹¹R¹², wherein R¹¹ and R¹² are, independently, selected from the group consisting of a hydrogen atom, C₁ to C₁₂ alkyl, C₁ to C₁₂ substituted alkyl, C₂ to C₁₂ alkenyl, C₂ to C₁₂

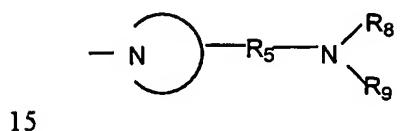
25 substituted alkenyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C₇ to C₁₈ phenylalkyl, C₇ to C₁₈ substituted phenylalkyl, C₁ to C₁₂ heterocycloalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted heterocycle;

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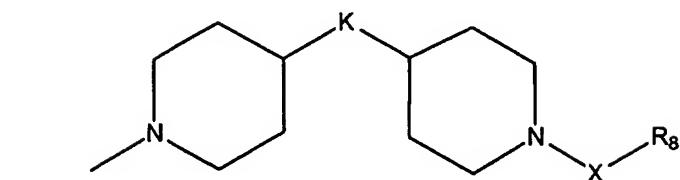
Z is the structure A:



10 or the structure B:



20 or the structure C:



wherein, in structure A, Q is the formula $((\text{CH}_2)_n\text{NH})_m$, where m is 0 or 1, n is 1 to 6 and the alkylene portion of Q is directly attached to the depicted nitrogen atom in
 30 structure A; and the dotted line between R₆ and R₇ indicates that R₆ and R₇ are optionally directly attached;

wherein, in structure B, the depicted cyclic portion is an unsubstituted or substituted heterocycle that is fully saturated, contains 4 to 7 ring atoms, 1 to 2 nitrogen rings atoms and 0 to 1 other heteroatoms selected from 5 oxygen and sulfur;

wherein, in structure C, K is absent or present and, if present, is a C₁ to C₁₂ alkylene;

- 10 R₅ is selected from the group consisting of C₁ to C₁₀ alkylene, C₂ to C₁₀ alkenylene, C₂ to C₁₀ alkynylene, C₁ to C₁₀ substituted alkylene, C₂ to C₁₀ substituted alkenylene, C₂ to C₁₀ substituted alkynylene, substituted epimino, C₁ to C₅ substituted alkylene epimino, thio, C₁ to C₁₀ alkylene thio, 15 C₁ to C₁₀ substituted alkylene thio, sulfonyl, C₁ to C₁₀ alkylene sulfonyl, C₁ to C₁₀ substituted alkylene sulfonyl, sulfinyl, C₁ to C₁₀ alkylene sulfinyl, C₁ to C₁₀ substituted alkylene sulfinyl, oxy, C₁ to C₁₀ alkylene oxy, C₁ to C₁₀ substituted alkylene oxy, C₁ to C₁₀ alkylene dioxy, C₁ to C₁₀ 20 substituted alkylene dioxy, C₁ to C₁₀ alkylene trioxy and C₁ to C₁₀ substituted alkylene trioxy;

X is absent or present and, if present, is selected from the group consisting of carbonyl, thiocarbonyl, thioester, 25 sulfonyl and sulfinyl;

where R₆ and R₇ are not directly attached to each other, they are independently selected from the group consisting of 30 a hydrogen atom, C₁ to C₁₂ alkyl, C₂ to C₁₂ alkenyl, C₂ to C₁₂ alkynyl, C₁ to C₁₂ substituted alkyl, C₂ to C₁₂ substituted

alkenyl, C₂ to C₁₂ substituted alkynyl, C₃ to C₇ cycloalkyl, C₃ to C₇ substituted cycloalkyl, C₅ to C₇ cycloalkenyl, C₅ to C₇ substituted cycloalkenyl, heterocyclic ring, substituted heterocyclic ring, C₇ to C₁₈ phenylalkyl, C₇ to C₁₈

5 substituted phenylalkyl, C₁ to C₁₂ heterocycloalkyl, C₁ to C₁₂ substituted heterocycloalkyl, cyclic C₂ to C₇ alkylene, substituted cyclic C₂ to C₇ alkylene, cyclic C₂ to C₇ heteroalkylene, substituted cyclic C₂ to C₇ heteroalkylene, hydroxymethyl and protected hydroxymethyl; or

10

where R₆ and R₇ are directly attached to each other are, collectively selected from the group consisting of C₁ to C₅ alkylene, C₂ to C₅ alkenylene, C₂ to C₅ alkynylene, C₁ to C₅ substituted alkylene, C₂ to C₅ substituted alkenylene, C₂ to

15 C₅ substituted alkynylene, substituted epimino, C₁ to C₅ substituted alkylene epimino, thio, C₁ to C₅ alkylene thio, C₁ to C₅ substituted alkylene thio, sulfonyl, C₁ to C₅ alkylene sulfonyl, C₁ to C₅ substituted alkylene sulfonyl, sulfinyl, C₁ to C₅ alkylene sulfinyl, C₁ to C₅ substituted

20 alkylene sulfinyl, oxy, C₁ to C₅ alkylene oxy, C₁ to C₅ substituted alkylene oxy, C₁ to C₅ alkylene dioxy, C₁ to C₅ substituted alkylene dioxy, C₁ to C₅ alkylene trioxy and C₁ to C₅ substituted alkylene trioxy; and

X is absent or present and, if present, is selected from the 25 group consisting of carbonyl, thiocarbonyl, thioester, sulfonyl and sulfinyl; and

R₈ and, if present, R₉ are independently selected from the group consisting of a hydrogen atom, C₁ to C₁₂ alkyl, C₂ to

30 C₁₂ alkenyl, C₂ to C₁₂ alkynyl, C₁ to C₁₂ substituted alkyl, C₂

to C₁₂ substituted alkenyl, C₂ to C₁₂ substituted alkynyl, C₃ to C₇ cycloalkyl, C₃ to C₇ substituted cycloalkyl, C₅ to C₇ cycloalkenyl, C₅ to C₇ substituted cycloalkenyl, heterocyclic ring, substituted heterocyclic ring, C₇ to C₁₈ phenylalkyl, C₇ to C₁₈ substituted phenylalkyl, C₁ to C₁₂ heterocycloalkyl, C₁ to C₁₂ substituted heterocycloalkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, cyclic C₂ to C₇ alkylene, substituted cyclic C₂ to C₇ alkylene, cyclic C₂ to C₇ heteroalkylene, substituted cyclic C₂ to C₇ heteroalkylene, protected hydroxymethyl, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, C₁ to C₁₀ alkylamino, C₁ to C₁₀ alkyl protected amino, C₁ to C₁₀ alkyl (monosubstituted)amino, C₁ to C₁₀ alkyl, protected (monosubstituted)amino, C₁ to C₁₀ alkyl(disubstituted)amino, C₁ to C₁₀ substituted alkylamino, C₁ to C₁₀ substituted alkyl protected amino, C₁ to C₁₀ substituted alkyl (monosubstituted)amino, C₁ to C₁₀ substituted alkyl protected (monosubstituted)amino, C₁ to C₁₀ substituted alkyl (disubstituted)amino, carboxamide, protected carboxamide, and the group consisting of (i) the formula -C(O)NR¹¹R¹², (ii) the formula -C(O)R¹¹, (iii) the formula -NR¹¹R¹², (iv) the formula -C(O)OR¹¹, wherein R¹¹ and R¹² are, independently, selected from the group consisting of a hydrogen atom, C₁ to C₁₂ alkyl, C₁ to C₁₂ substituted alkyl, C₂ to C₁₂ alkenyl, C₂ to C₁₂ substituted alkenyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C₇ to C₁₈ phenylalkyl, C₇ to C₁₈ substituted phenylalkyl, C₁ to C₁₂ heterocycloalkyl, C₁ to C₁₂ substituted heterocycloalkyl, heteroaryl, substituted heteroaryl, heterocycle, substituted

heterocycle, C₁ to C₁₂ acyl, C₁ to C₁₂ substituted acyl, phenylsulfonyl, substituted phenylsulfonyl, C₁ to C₁₀ alkylsulfonyl, C₁ to C₁₀ substituted alkylsulfonyl, C₁ to C₁₂ alkylaminocarbonyl, C₁ to C₁₂ substituted alkylaminocarbonyl, 5 phenylaminocarbonyl, and substituted phenylaminocarbonyl; or

R₈ and R₉, together with the adjoining nitrogen depicted in structure B are, collectively, selected from the group consisting of heterocycle and substituted heterocycle;

10

provided that, if X is carbonyl, R₈ is not alkoxy; and

provided that X can only be absent where R₆ and R₇ are not directly attached to each other; or

15

a salt of said compound.

2. The single compound of claim 1, wherein:

20 R₁ and R₄ are independently selected from the group consisting of a hydrogen atom, halo, C₁ to C₁₂ alkyl and C₁ to C₁₂ substituted alkyl.

3. The single compound of claim 1, wherein:

25 one of R₂ and R₃ is selected from the group consisting of a hydrogen atom, halo, C₁ to C₁₂ alkyl and C₁ to C₁₂ substituted alkyl; and the other of R₂ and R₃ is selected from the group consisting of hydrogen atom, halo, hydroxy, 30 carboxy, thio, carboxamide, the formula -C(O)NR¹¹R¹² and the formula S(O)₂NR¹¹R¹², wherein R¹¹ and R¹² are, independently,

selected from the group consisting of a hydrogen atom, C₁ to C₁₂ alkyl, C₁ to C₁₂ substituted alkyl, C₂ to C₁₂ alkenyl, C₂ to C₁₂ substituted alkenyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C₇ to C₁₈ phenylalkyl, C₇ to 5 C₁₈ substituted phenylalkyl, C₁ to C₁₂ heterocycloalkyl and C₁ to C₁₂ substituted heterocycloalkyl.

4. The single compound of claim 1, wherein R₆ and R₇ are not directly attached to each other and are independently 10 selected from the group consisting of a hydrogen atom, C₁ to C₁₂ alkyl, C₁ to C₁₂ substituted alkyl, C₃ to C₇ cycloalkyl and C₃ to C₇ substituted cycloalkyl.

5. The single compound of claim 1, wherein: 15 R₈ and, if present, R₉ are independently selected from the group consisting of a hydrogen atom, C₁ to C₁₂ alkyl, C₂ to C₁₂ alkenyl, C₂ to C₁₂ alkynyl, C₁ to C₁₂ substituted alkyl, C₂ to C₁₂ substituted alkenyl, C₃ to C₇ cycloalkyl, C₃ to C₇ 20 substituted cycloalkyl, C₅ to C₇ cycloalkenyl, C₅ to C₇ substituted cycloalkenyl, heterocyclic ring, substituted heterocyclic ring, C₇ to C₁₈ phenylalkyl, C₇ to C₁₈ substituted phenylalkyl, C₁ to C₁₂ heterocycloalkyl, C₁ to C₁₂ substituted heterocycloalkyl, phenyl, substituted phenyl, 25 cyclic C₂ to C₇ alkylene, substituted cyclic C₂ to C₇ alkylene, cyclic C₂ to C₇ heteroalkylene and substituted cyclic C₂ to C₇ heteroalkylene; or

R_8 and R_9 , together with the adjoining nitrogen depicted in structure B are, collectively, selected from the group consisting of heterocycle and substituted heterocycle.

5 6. The single compound of claim 1, wherein R_5 is selected from the group consisting of C_1 to C_8 alkylene and C_1 to C_8 substituted alkylene.

10 7. The single compound of claim 1, wherein R_6 and R_7 are directly attached to each other and are, collectively, selected from the group consisting of C_1 to C_5 alkylene and C_1 to C_5 substituted alkylene.

15 8. The single compound of claim 1, wherein X is absent.

9. The single compound of claim 1, wherein X is selected from the group consisting of carbonyl and sulfonyl.

10. The single compound of claim 1, wherein:

20 R_1 and R_4 , and one of R_2 and R_3 , are independently selected from the group consisting of a hydrogen atom, halo, protected hydroxy, cyano, C_1 to C_{12} alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} alkynyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} substituted alkenyl, C_2 to C_{12} substituted alkynyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkoxy, phenyl, substituted phenyl, (disubstituted)amino, C_1 to C_{10} alkylthio and C_1 to C_{10} substituted alkylthio;

25 30 the other of R_2 and R_3 is selected from the group consisting of a hydrogen atom, halo, hydroxy, carboxy, thio,

carboxamide, the formula $-C(O)NR^{11}R^{12}$ and the formula $S(O)_2NR^{11}R^{12}$, wherein R^{11} and R^{12} are, independently, selected from the group consisting of a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} substituted alkenyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocycloalkyl and C_1 to C_{12} substituted heterocycloalkyl; and

5 where R_6 and R_7 are not directly attached to each other, are independently selected from the group consisting of a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_3 to C_7 cycloalkyl and C_3 to C_7 substituted cycloalkyl;

10 R_8 and, if present, R_9 are independently selected from the group consisting of a hydrogen atom, C_1 to C_{12} alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} alkynyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} substituted alkenyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, heterocyclic ring, substituted heterocyclic ring, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocycloalkyl, C_1 to C_{12} substituted heterocycloalkyl, phenyl, substituted phenyl, cyclic C_2 to C_7 alkylene, substituted cyclic C_2 to C_7 alkylene, cyclic C_2 to C_7 heteroalkylene and substituted cyclic C_2 to C_7 heteroalkylene; or

15 R_8 and R_9 , together with the adjoining nitrogen depicted in structure B are, collectively, selected from the group consisting of heterocycle and substituted heterocycle; and

20

25

30

R_5 is selected from the group consisting of C_1 to C_8 alkylene and C_1 to C_8 substituted alkylene;

5 where R_6 and R_7 are directly attached to each other, they are, collectively, selected from the group consisting of C_1 to C_5 alkylene and C_1 to C_5 substituted alkylene; and

X is absent or present and, if present, is selected from the group consisting of carbonyl and sulfonyl.

10

11. The compound of claim 1, wherein Z is the structure A.

12. The compound of claim 1, wherein Z is the structure B.

15 13. The compound of claim 11, wherein R_6 and R_7 are directly attached to each other.

14. The compound of claim 11, wherein R_6 and R_7 are not directly attached to each other.

20

15. The compound of claim 11, wherein the cyclic portion of structure A is selected from the group consisting of 1,4-piperazine and 1,4-homopiperazine.

25 16. The compound of claim 1, wherein:

R_1 and R_4 are each hydrogen; and

30 one of R_2 and R_3 is hydrogen and the other is the formula $-C(O)NR^{11}R^{12}$, wherein one of R^{11} and R^{12} is hydrogen and the

other is selected from the group consisting of 2-morpholin-4-yl-ethyl, 3-pyrrolidin-1-yl-propyl, allyl, 3-fluorobenzyl, 2-piperidin-1-yl-ethyl, 4-morpholino-3-propyl, ethyl-4-butyryl, 2-methoxyethyl, benzyl, 4-methylbenzyl, N,N-diethylethylene, N,N-diethyl-1,3-propylene, 3,5-dimethoxybenzyl, 4-fluorophenethyl, 4-fluorobenzyl, 2-fluorophenethyl, 2-(3,4-dimethoxyphenyl)ethyl, 2-pyridin-2-yl-ethyl, propargyl, 2-pyrrolidin-1-yl-ethyl, 2-chlorobenzyl, cyclopropyl, 10 pyridin-3-yl-methyl, 2-thiophenemethyl, 3-(methylthio)propyl, cyclohexanemethyl, 2-ethoxyethyl, cyclopentyl, cyclohexyl, 3-chlorobenzyl, 4-methoxyphenethyl, 2-(4-chlorophenyl)ethyl, 3-dimethylamino-1-propyl, 3,4-dimethoxybenzyl, 2-bromobenzyl, N-(3-propyl)-15 N-methylaniline, 2-propionic acid, 2-(3-phenyl)-propionic acid, 2-(4-methyl)-pentanoic acid, (±)-tetrahydrofuryl, 3-imidazol-1-yl-propyl, 2-trifluoromethylbenzyl, cycloheptyl, 2,4-dichlorophenethyl, 1-(3-propyl)-pyrrolidin-2-one, 4-tert-butylcyclohexyl, 2,2,6,6-20 tetramethyl-piperidin-4-yl, 5-diethylamino-2-pentyl, 1,3-dimethylbutyl, 2,4-dimethylbenzyl, thiophene-2-ethyl, 4-methoxyphenyl, 4-piperidino-1-carboxylic acid ethyl ester, 3-methoxybenzyl, N-1-ethyl-N-1-m-tolyl-2-ethyl, 1-benzyl-piperidin-4-yl, 1-methyl-3-phenylpropyl, 2-25 fluorobenzyl, 3-(trifluoromethyl)benzyl, piperonyl, 1-naphthalenemethyl, 3,4-dichlorobenzyl, (R)-(-)-1-cyclohexylethyl, (+/-)-1-(1-naphthyl)ethyl, 4-(trifluoromethoxy)benzyl and 5-guanidinopentanoic acid-2-yl.

17. The single compound of claim 16, wherein:

Z is the structure A or the structure C, wherein:

5 X is carbonyl and the combination of X-R₈ is selected from the group consisting of benzoyl, methoxyacetyl, tert-butylacetyl, 2,4-difluorobenzoyl, 2,4-dimethylbenzoyl, 2-ethylhexanoyl, 2-propylpentanoyl, 3-indolepropionyl, N-phenylanthranilyl, trans-2-carboxycyclohexanoyl, cyclohex-3-en-oyl, trans-pent-2-en-oyl, 1-methyl-1-cyclohexanoyl, 1-acetylpiridine-4-carbonyl, cyclopropanecarbonyl, methanesulfonylacetyl, 5-hexynoyl, 3-furoyl, 3,4-difluorophenylacetyl, 3-benzoyl-benzoyl, 2-(trifluoromethyl)phenylacetyl, 4-(trifluoromethyl)phenylacetyl, 2-acetylamo-3-(1H-indol-3-yl)-propionyl, 3-(phenylsulfonyl)propionyl, 2-benzyloxyphenylacetyl, benzo(b)thiophene-3-acetyl, 3-fluoro-2-methyl-benzoyl, 1-methylcyclopropane-1-carboxyl, (-)-menthoxyacetyl, cyclohexyl-1-acetic acid-1-methylcarbonyl, 2-(3-trifluoromethyl-phenylamino)-benzoyl, 2-ketobutyryl, 2-ethyl-2-hydroxybutyryl, 5-chlorovaleryl, 1-acetyl-pyrrolidine-2-carbonyl, 5-chlorothiophene-2-carboxylyl, 2-(2-methoxyethoxy)acetyl, 2-methyl-3-furoyl, 6-heptynoyl, 5-methylisoxazole-4-carbonyl; or

25

X is sulfonyl and the combination of X-R₈ is selected from the group consisting of 2-mesitylenesulfonyl, 2-naphthenesulfonyl, 2-thiophenesulfonyl, 4-chlorobenzenesulfonyl, 4-fluorobenzenesulfonyl, N-acetylsulfanilyl, 2-acetamide-4-methyl-5-thiazolesulfonyl,

30

4-tert-butylbenzenesulfonyl, 8-quinolinesulfonyl, 3-chloro-4-fluorobenzenesulphonyl, 4-ethylbenzenesulfonyl, pentamethylbenzenesulfonyl, 2,4-dichlorobenzenesulphonyl, 2-chloro-6-methylbenzenesulphonyl, 3,4-
5 difluorobenzenesulphonyl, 3,5-dichlorobenzenesulfonyl, 3-chlorobenzenesulfonyl, 3-fluorobenzenesulphonyl, 4-trifluoromethylbenzenesulphonyl,
2-(methoxycarbonyl)thiophene-3-sulfonyl, 1-methylimidazole-4-sulfonyl, 3-chloro-4-methylbenzenesulfonyl, 4-
10 isopropylbenzenesulphonyl, 3,4-dichlorobenzenesulfonyl, 1-naphthalenesulfonyl, 3-nitrobenzenesulfonyl, 4-bromobenzenesulfonyl, 4-nitrobenzenesulfonyl, 2,3,5,6-tetramethylbenzenesulfonyl, p-xylene-2-sulfonyl,
4-n-propylbenzenesulfonyl, 4-n-amylbenzenesulfonyl,
15 2-chlorobenzenesulfonyl, 5-chlorothiophene-2-sulfonyl, m-toluenesulfonyl, 2-bromobenzenesulfonyl, p-styrenesulfonyl, 4-pentylbenzene-1-sulfonyl,
4-n-butylbenzenesulfonyl and 2-methylsulfonylbenzenesulfonyl.
20

18. The compound of claim 17, wherein:

Z is the structure A, wherein:

25 *m* is 0;

*R*₅ is selected from the group consisting of 1,4-butylene, 1,2-ethylene and 1,3-propylene;

R₆ and R₇ are directly attached and, combined, is 1,2-ethylene; or R₆ and R₇ are not directly attached and are each selected from the group consisting of hydrogen and ethyl.

5

19. The compound of claim 17, wherein:

Z is structure A, wherein:

10 m is 1;

n is 3;

R₅ is 1,2-ethylene; and

15

R₆ and R₇ are directly attached and, combined, is 1,2-ethylene.

20. The compound of claim 17, wherein:

20

Z is structure C, wherein:

K is absent or, if present, is 1,3-propylene.

25 21. The compound of claim 16, wherein Z is structure B.

22. The compound of claim 21, wherein the cyclic portion of structure B is selected from the group consisting of pyrrolidine, piperidine and piperazine.

30

23. The compound of claim 22, wherein:

the cyclic portion of structure B is selected from the group consisting of 1,2-pyrrolidene, 1,2-piperidene and 5 1,4-piperazene, wherein R₅ is directly connected at the 2-position, 2-position and 4-position, respectively,

R₅ is selected from the group consisting of methylene and ethylene; and

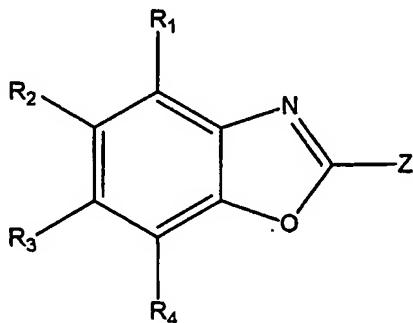
10

R₈ and R₉ are, independently selected from the group consisting of hydrogen, methyl, ethyl, hydroxyethyl, benzyl, cyclohexyl, isobutyl, propyl, butyl, sec-butyl, hexyl, heptyl, allyl, cyanoethyl, 2-picolyl, 15 cyclohexylmethyl, cyclohexylethane-1,1-diyl, N,N-diethylaminoethyl, N,N-dimethylaminopropyl and neopentyl; or

R₈ and R₉, together with the adjoining nitrogen atom 20 depicted in structure B are, collectively, selected from the group consisting of pyrrolidin-1-yl, piperidin-1-yl, 3-(carboxamide)piperidin-1-yl, 2-(carboxamide)pyrrolidin-1-yl, 4-(methyl)piperazin-1-yl, morpholin-4-yl, 2-(hydroxymethyl)piperidin-1-yl, 4- 25 (ethylcarboxylate)piperidin-1-yl, 4-(phenyl)piperazin-1-yl, 4-(2-pyrimidyl)-piperazin-1-yl, thiomorpholin-4-yl, 4-(benzyl)piperazin-1-yl, 3-(ethylcarboxylate)piperidin-1-yl, 4-(hydroxy)piperidin-1-yl, 3,5-(dimethyl)piperazin-1-yl, 4-homopiperazin-1-yl, 4-(methyl)homopiperazin-1-yl, 2- 30 (methyl)piperidin-1-yl, 3,5-(dimethyl)piperidin-1-yl, 3-

(N,N-dimethylamino)pyrrolidin-1-yl, 3-(amino)pyrrolidin-1-yl, homopiperidin-1-yl, decahydroquinolin-1-yl and tetrahydroisoquinolin-1-yl.

5 24. A combinatorial library of two or more compounds of the structure:



10

wherein R₁ and R₄, and one of R₂ and R₃, are independently selected from the group consisting of a hydrogen atom, halo, hydroxy, protected hydroxy, cyano, C₁ to C₁₂ alkyl, C₂ to C₁₂ alkenyl, C₂ to C₁₂ alkynyl, C₁ to C₁₂ substituted alkyl, C₂ to C₁₂ substituted alkenyl, C₂ to C₁₂ substituted alkynyl, C₁ to C₁₂ alkoxy, C₁ to C₁₂ substituted alkoxy, C₁ to C₁₂ acyloxy, C₁ to C₁₂ acyl, C₃ to C₇ cycloalkyl, C₃ to C₇ substituted cycloalkyl, C₅ to C₇ cycloalkenyl, C₅ to C₇ substituted cycloalkenyl, heterocyclic ring, substituted heterocyclic ring, C₇ to C₁₈ phenylalkyl, C₇ to C₁₈ substituted phenylalkyl, C₁ to C₁₂ heterocycloalkyl, C₁ to C₁₂ substituted heterocycloalkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, cyclic C₂ to C₇ alkylene, substituted cyclic C₂ to C₇ alkylene, cyclic C₂ to C₇ heteroalkylene, substituted cyclic C₂ to C₇

heteroalkylene, carboxy, protected carboxy, hydroxymethyl, protected hydroxymethyl, protected amino, protected (monosubstituted) amino, (disubstituted) amino, C₁ to C₁₀ alkyl protected amino, C₁ to C₁₀ alkyl protected

5 (monosubstituted) amino, C₁ to C₁₀ alkyl (disubstituted) amino, C₁ to C₁₀ substituted alkylamino, C₁ to C₁₀ substituted alkyl protected (monosubstituted) amino, C₁ to C₁₀ substituted alkyl (disubstituted) amino, carboxamide, C₁ to C₁₀ alkylthio, C₁ to C₁₀ substituted alkylthio, C₁ to C₁₀ alkylsulfonyl, C₁ to C₁₀ substituted alkylsulfonyl, C₁ to C₁₀ alkylsulfoxide, C₁ to C₁₀ substituted alkylsulfoxide, phenylthio, substituted phenylthio, phenylsulfoxide, substituted phenylsulfoxide, phenylsulfonyl, substituted phenylsulfonyl and the group consisting of (i) the formula -C(O)NR¹¹R¹²,

15 (ii) the formula -SR¹¹, (iii) the formula -OR¹¹ and (iv) the formula -C(O)OR¹¹, wherein R¹¹ and R¹² are, independently, selected from the group consisting of a hydrogen atom, C₁ to C₁₂ alkyl, C₁ to C₁₂ substituted alkyl, C₂ to C₁₂ alkenyl, C₂ to C₁₂ substituted alkenyl, phenyl, substituted phenyl, 20 naphthyl, substituted naphthyl, C₇ to C₁₈ phenylalkyl, C₇ to C₁₈ substituted phenylalkyl, C₁ to C₁₂ heterocycloalkyl, C₁ to C₁₂ substituted heterocycloalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted heterocycle;

25 the other of R₂ and R₃ is selected from the group consisting of a hydrogen atom, halo, hydroxy, protected hydroxy, carboxy, thio, C₁ to C₁₂ alkyl, C₂ to C₁₂ alkenyl, C₂ to C₁₂ alkynyl, C₁ to C₁₂ substituted alkyl, C₂ to C₁₂ substituted alkenyl, C₂ to C₁₂ substituted alkynyl, C₁ to C₁₂ alkoxy, C₁ to C₁₂ substituted alkoxy, C₁ to C₁₂ acyloxy, C₁ to C₁₂ acyl,

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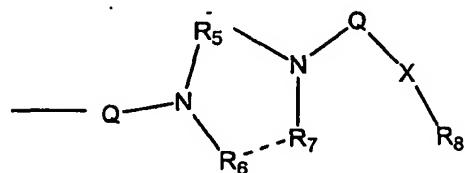
C₃ to C₇ cycloalkyl, C₃ to C₇ substituted cycloalkyl, C₅ to C₇ cycloalkenyl, C₅ to C₇ substituted cycloalkenyl, heterocyclic ring, substituted heterocyclic ring, C₇ to C₁₈ phenylalkyl, C₇ to C₁₈ substituted phenylalkyl, C₁ to C₁₂ heterocycloalkyl, C₁ to C₁₂ substituted heterocycloalkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, cyclic C₂ to C₇ alkylene, substituted cyclic C₂ to C₇ alkylene, cyclic C₂ to C₇ heteroalkylene, substituted cyclic C₂ to C₇ heteroalkylene, carboxy, protected carboxy, hydroxymethyl, protected hydroxymethyl, protected amino, protected (monosubstituted) amino, (disubstituted) amino, C₁ to C₁₀ alkyl protected amino, C₁ to C₁₀ alkyl protected (monosubstituted) amino, C₁ to C₁₀ alkyl (disubstituted) amino, C₁ to C₁₀ substituted alkyl protected amino, C₁ to C₁₀ substituted alkyl protected (monosubstituted) amino, C₁ to C₁₀ substituted alkyl (disubstituted) amino, carboxamide, C₁ to C₁₀ alkylthio, C₁ to C₁₀ substituted alkylthio, C₁ to C₁₀ alkylsulfonyl, C₁ to C₁₀ substituted alkylsulfonyl, C₁ to C₁₀ alkylsulfoxide, C₁ to C₁₀ substituted alkylsulfoxide, phenylthio, substituted phenylthio, phenylsulfoxide, substituted phenylsulfoxide, phenylsulfonyl, substituted phenylsulfonyl and the group consisting of (i) the formula -C(O)NR¹¹R¹², (ii) the formula -SR¹¹, (iii) the formula -OR¹¹, (iv) the formula -C(O)OR¹¹ and (v) the formula S(O)₂NR¹¹R¹², wherein R¹¹ and R¹² are, independently, selected from the group consisting of a hydrogen atom, C₁ to C₁₂ alkyl, C₁ to C₁₂ substituted alkyl, C₂ to C₁₂ alkenyl, C₂ to C₁₂ substituted alkenyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C₇ to C₁₈ phenylalkyl, C₇ to C₁₈ substituted phenylalkyl, C₁ to C₁₂ heterocycloalkyl, C₁ to

120

C_{12} substituted heterocycloalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted heterocycle;

Z is the structure A:

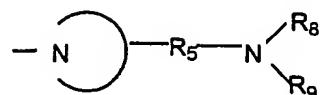
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or the structure B:

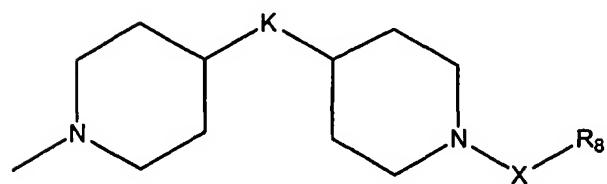
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20

or the structure C:

25



30 wherein, in structure A, Q is the formula $((CH_2)_nNH)_m$, where m is 0 or 1, n is 1 to 6 and the alkylene portion of Q is directly attached to the depicted nitrogen atom in

structure A; and the dotted line between R₆ and R₇ indicates that R₆ and R₇ are optionally directly attached;

wherein, in structure B, the depicted cyclic portion is an

5 unsubstituted or substituted heterocycle that is fully saturated, contains 4 to 7 ring atoms, 1 to 2 nitrogen rings atoms and 0 to 1 other heteroatoms selected from oxygen and sulfur;

10 wherein, in structure C, K is absent or present and, if present, is a C₁ to C₁₂ alkylene;

R₅ is selected from the group consisting of C₁ to C₁₀ alkylene, C₂ to C₁₀ alkenylene, C₂ to C₁₀ alkynylene, C₁ to C₁₀ substituted alkylene, C₂ to C₁₀ substituted alkenylene, C₂ to C₁₀ substituted alkynylene, substituted epimino, C₁ to C₅ substituted alkylene epimino, thio, C₁ to C₁₀ alkylene thio, C₁ to C₁₀ substituted alkylene thio, sulfonyl, C₁ to C₁₀ alkylene sulfonyl, C₁ to C₁₀ substituted alkylene sulfonyl,

20 sulfinyl, C₁ to C₁₀ alkylene sulfinyl, C₁ to C₁₀ substituted alkylene sulfinyl, oxy, C₁ to C₁₀ alkylene oxy, C₁ to C₁₀ substituted alkylene oxy, C₁ to C₁₀ alkylene dioxy, C₁ to C₁₀ substituted alkylene dioxy, C₁ to C₁₀ alkylene trioxy and C₁ to C₁₀ substituted alkylene trioxy;

25 X is absent or present and, if present, is selected from the group consisting of carbonyl, thiocarbonyl, thioester, sulfonyl and sulfinyl;

30 where R₆ and R₇ are not directly attached to each other, they are independently selected from the group consisting of

a hydrogen atom, C₁ to C₁₂ alkyl, C₂ to C₁₂ alkenyl, C₂ to C₁₂ alkynyl, C₁ to C₁₂ substituted alkyl, C₂ to C₁₂ substituted alkenyl, C₂ to C₁₂ substituted alkynyl, C₃ to C₇ cycloalkyl, C₃ to C₇ substituted cycloalkyl, C₅ to C₇ cycloalkenyl, C₅ to C₇ substituted cycloalkenyl, heterocyclic ring, substituted heterocyclic ring, C₇ to C₁₈ phenylalkyl, C₇ to C₁₈ substituted phenylalkyl, C₁ to C₁₂ heterocycloalkyl, C₁ to C₁₂ substituted heterocycloalkyl, cyclic C₂ to C₇ alkylene, substituted cyclic C₂ to C₇ alkylene, cyclic C₂ to C₇ heteroalkylene, substituted cyclic C₂ to C₇ heteroalkylene, hydroxymethyl and protected hydroxymethyl; or

where R₆ and R₇ are directly attached to each other are, collectively selected from the group consisting of C₁ to C₅ alkylene, C₂ to C₅ alkenylene, C₂ to C₅ alkynylene, C₁ to C₅ substituted alkylene, C₂ to C₅ substituted alkenylene, C₂ to C₅ substituted alkynylene, substituted epimino, C₁ to C₅ substituted alkylene epimino, thio, C₁ to C₅ alkylene thio, C₁ to C₅ substituted alkylene thio, sulfonyl, C₁ to C₅ alkylene sulfonyl, C₁ to C₅ substituted alkylene sulfonyl, sulfinyl, C₁ to C₅ alkylene sulfinyl, C₁ to C₅ substituted alkylene sulfinyl, oxy, C₁ to C₅ alkylene oxy, C₁ to C₅ substituted alkylene oxy, C₁ to C₅ alkylene dioxy, C₁ to C₅ substituted alkylene dioxy, C₁ to C₅ alkylene trioxy and C₁ to C₅ substituted alkylene trioxy; and

X is absent or present and, if present, is selected from the group consisting of carbonyl, thiocarbonyl, thioester, sulfonyl and sulfinyl; and

R₈ and, if present, R₉ are independently selected from the group consisting of a hydrogen atom, C₁ to C₁₂ alkyl, C₂ to C₁₂ alkenyl, C₂ to C₁₂ alkynyl, C₁ to C₁₂ substituted alkyl, C₂ to C₁₂ substituted alkenyl, C₂ to C₁₂ substituted alkynyl, C₃ to C₇ cycloalkyl, C₃ to C₇ substituted cycloalkyl, C₅ to C₇ cycloalkenyl, C₅ to C₇ substituted cycloalkenyl, heterocyclic ring, substituted heterocyclic ring, C₇ to C₁₈ phenylalkyl, C₇ to C₁₈ substituted phenylalkyl, C₁ to C₁₂ heterocycloalkyl, C₁ to C₁₂ substituted heterocycloalkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, cyclic C₂ to C₇ alkylene, substituted cyclic C₂ to C₇ alkylene, cyclic C₂ to C₇ heteroalkylene, substituted cyclic C₂ to C₇ heteroalkylene, protected hydroxymethyl, protected amino, (monosubstituted)amino, protected (15) (monosubstituted)amino, (disubstituted)amino, C₁ to C₁₀ alkylamino, C₁ to C₁₀ alkyl protected amino, C₁ to C₁₀ alkyl (monosubstituted)amino, C₁ to C₁₀ alkyl, protected (monosubstituted)amino, C₁ to C₁₀ alkyl (disubstituted)amino, C₁ to C₁₀ substituted alkylamino, C₁ to C₁₀ substituted alkyl (20) protected amino, C₁ to C₁₀ substituted alkyl (monosubstituted)amino, C₁ to C₁₀ substituted alkyl protected (monosubstituted)amino, C₁ to C₁₀ substituted alkyl (disubstituted)amino, carboxamide, protected carboxamide, and the group consisting of (i) the formula -C(O)NR¹¹R¹², (ii) the formula -C(O)R¹¹, (iii) the formula -NR¹¹R¹², (iv) the formula -C(O)OR¹¹, wherein R¹¹ and R¹² are, 25 independently, selected from the group consisting of a hydrogen atom, C₁ to C₁₂ alkyl, C₁ to C₁₂ substituted alkyl, C₂ to C₁₂ alkenyl, C₂ to C₁₂ substituted alkenyl, phenyl, (30) substituted phenyl, naphthyl, substituted naphthyl, C₇ to C₁₈

phenylalkyl, C₇ to C₁₈ substituted phenylalkyl, C₁ to C₁₂ heterocycloalkyl, C₁ to C₁₂ substituted heterocycloalkyl, heteroaryl, substituted heteroaryl, heterocycle, substituted heterocycle, C₁ to C₁₂ acyl, C₁ to C₁₂ substituted acyl,
5 phenylsulfonyl, substituted phenylsulfonyl, C₁ to C₁₀ alkylsulfonyl, C₁ to C₁₀ substituted alkylsulfonyl, C₁ to C₁₂ alkylaminocarbonyl, C₁ to C₁₂ substituted alkylaminocarbonyl, phenylaminocarbonyl, and substituted phenylaminocarbonyl; or

10 R₈ and R₉, together with the adjoining nitrogen depicted in structure B are, collectively, selected from the group consisting of heterocycle and substituted heterocycle;

provided that, if X is carbonyl, R₈ is not alkoxy; and
15 provided that X can only be absent where R₆ and R₇ are not directly attached to each other; or

a salt of said compound.
20

25. The combinatorial library of claim 24, wherein: R₁ and R₄ are independently selected from the group consisting of a hydrogen atom, halo, C₁ to C₁₂ alkyl and C₁ to C₁₂ substituted alkyl.

25

26. The combinatorial library of claim 24, wherein:
one of R₂ and R₃ is selected from the group consisting of a hydrogen atom, halo, C₁ to C₁₂ alkyl and C₁ to C₁₂ substituted alkyl; and the other of R₂ and R₃ is selected from the group consisting of hydrogen atom, halo, hydroxy,
30

carboxy, thio, carboxamide, the formula $-C(O)NR^{11}R^{12}$ and the formula $S(O)_2NR^{11}R^{12}$, wherein R^{11} and R^{12} are, independently, selected from the group consisting of a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} substituted alkenyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocycloalkyl and C_1 to C_{12} substituted heterocycloalkyl.

10 27. The combinatorial library of claim 24, wherein R_6 and R_7 are not directly attached to each other and are independently selected from the group consisting of a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_3 to C_7 cycloalkyl and C_3 to C_7 substituted cycloalkyl.

15 28. The combinatorial library of claim 24, wherein: R_8 and, if present, R_9 are independently selected from the group consisting of a hydrogen atom, C_1 to C_{12} alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} alkynyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} substituted alkenyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, heterocyclic ring, substituted heterocyclic ring, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocycloalkyl, C_1 to C_{12} substituted heterocycloalkyl, phenyl, substituted phenyl, cyclic C_2 to C_7 alkylene, substituted cyclic C_2 to C_7 alkylene, cyclic C_2 to C_7 heteroalkylene and substituted cyclic C_2 to C_7 heteroalkylene; or

R_8 and R_9 , together with the adjoining nitrogen depicted in structure B are, collectively, selected from the group consisting of heterocycle and substituted heterocycle.

5 29. The combinatorial library of claim 24, wherein R_5 is selected from the group consisting of C_1 to C_8 alkylene and C_1 to C_8 substituted alkylene.

10 30. The combinatorial library of claim 24, wherein R_6 and R_7 are directly attached to each other and are, collectively, selected from the group consisting of C_1 to C_5 alkylene and C_1 to C_5 substituted alkylene.

15 31. The combinatorial library of claim 24, wherein X is absent.

32. The combinatorial library of claim 24, wherein X is selected from the group consisting of carbonyl and sulfonyl.

20 33. The combinatorial library of claim 24, wherein:

R_1 and R_4 , and one of R_2 and R_3 , are independently selected from the group consisting of a hydrogen atom, halo, protected hydroxy, cyano, C_1 to C_{12} alkyl, C_2 to C_{12} alkenyl, $25 C_2$ to C_{12} alkynyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} substituted alkenyl, C_2 to C_{12} substituted alkynyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkoxy, phenyl, substituted phenyl, (disubstituted)amino, C_1 to C_{10} alkylthio and C_1 to C_{10} substituted alkylthio;

the other of R₂ and R₃ is selected from the group consisting of a hydrogen atom, halo, hydroxy, carboxy, thio, carboxamide, the formula -C(O)NR¹¹R¹² and the formula S(O)₂NR¹¹R¹², wherein R¹¹ and R¹² are, independently, selected

5 from the group consisting of a hydrogen atom, C₁ to C₁₂ alkyl, C₁ to C₁₂ substituted alkyl, C₂ to C₁₂ alkenyl, C₂ to C₁₂ substituted alkenyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C₇ to C₁₈ phenylalkyl, C₇ to C₁₈ substituted phenylalkyl, C₁ to C₁₂ heterocycloalkyl and

10 C₁ to C₁₂ substituted heterocycloalkyl; and

where R₆ and R₇ are not directly attached to each other, are independently selected from the group consisting of a hydrogen atom, C₁ to C₁₂ alkyl, C₁ to C₁₂ substituted alkyl,

15 C₃ to C₇ cycloalkyl and C₃ to C₇ substituted cycloalkyl;

R₈ and, if present, R₉ are independently selected from the group consisting of a hydrogen atom, C₁ to C₁₂ alkyl, C₂ to C₁₂ alkenyl, C₂ to C₁₂ alkynyl, C₁ to C₁₂ substituted alkyl, C₂ to C₁₂ substituted alkenyl, C₃ to C₇ cycloalkyl, C₃ to C₇ substituted cycloalkyl, C₅ to C₇ cycloalkenyl, C₅ to C₇ substituted cycloalkenyl, heterocyclic ring, substituted heterocyclic ring, C₇ to C₁₈ phenylalkyl, C₇ to C₁₈ substituted phenylalkyl, C₁ to C₁₂ heterocycloalkyl, C₁ to C₁₂ substituted heterocycloalkyl, phenyl, substituted phenyl,

20 cyclic C₂ to C₇ alkylene, substituted cyclic C₂ to C₇ alkylene, cyclic C₂ to C₇ heteroalkylene and substituted cyclic C₂ to C₇ heteroalkylene; or

25

R_8 and R_9 , together with the adjoining nitrogen depicted in structure B are, collectively, selected from the group consisting of heterocycle and substituted heterocycle; and

5 R_5 is selected from the group consisting of C_1 to C_8 alkylene and C_1 to C_8 substituted alkylene;

where R_6 and R_7 are directly attached to each other, they are, collectively, selected from the group consisting of C_1 to C_5 alkylene and C_1 to C_5 substituted alkylene; and

10 X is absent or present and, if present, is selected from the group consisting of carbonyl and sulfonyl.

15 34. The combinatorial library of claim 24, wherein Z is the structure A.

35. The combinatorial library of claim 24, wherein Z is the structure B.

20 36. The combinatorial library of claim 34, wherein R_6 and R_7 are directly attached to each other.

37. The combinatorial library of claim 34, wherein R_6 and R_7 are not directly attached to each other.

25

38. The combinatorial library of claim 34, wherein the cyclic portion of structure A is selected from the group consisting of 1,4-piperazine and 1,4-homopiperazine.

30 39. The combinatorial library of claim 24, wherein:

R₁ and R₄ are each hydrogen; and

one of R₂ and R₃ is hydrogen and the other is the formula

5 -C(O)NR¹¹R¹², wherein one of R¹¹ and R¹² is hydrogen and the other is selected from the group consisting of 2-morpholin-4-yl-ethyl, 3-pyrrolidin-1-yl-propyl, allyl, 3-fluorobenzyl, 2-piperidin-1-yl-ethyl, 4-morpholino-3-propyl, ethyl-4-butyryl, 2-methoxyethyl, benzyl, 4-methylbenzyl, N,N-diethylethylene, N,N-diethyl-1,3-propylene, 3,5-dimethoxybenzyl, 4-fluorophenethyl, 4-fluorobenzyl, 2-fluorophenethyl, 2-(3,4-dimethoxyphenyl)ethyl, 2-pyridin-2-yl-ethyl, propargyl, 2-pyrrolidin-1-yl-ethyl, 2-chlorobenzyl, cyclopropyl,

10 pyridin-3-yl-methyl, 2-thiophenemethyl, 3-(methylthio)propyl, cyclohexanemethyl, 2-ethoxyethyl, cyclopentyl, cyclohexyl, 3-chlorobenzyl, 4-methoxyphenethyl, 2-(4-chlorophenyl)ethyl, 3-dimethylamino-1-propyl, 3,4-dimethoxybenzyl, 2-bromobenzyl, N-(3-propyl)-

15 N-methylaniline, 2-propionic acid, 2-(3-phenyl)-propionic acid, 2-(4-methyl)-pentanoic acid, (±)-tetrahydrofuryl, 3-imidazol-1-yl-propyl, 2-trifluoromethylbenzyl, cycloheptyl, 2,4-dichlorophenethyl, 1-(3-propyl)-pyrrolidin-2-one, 4-tert-butylcyclohexyl, 2,2,6,6-tetramethyl-piperidin-4-yl, 5-diethylamino-2-pentyl,

20 1,3-dimethylbutyl, 2,4-dimethylbenzyl, thiophene-2-ethyl, 4-methoxyphenyl, 4-piperidino-1-carboxylic acid ethyl ester, 3-methoxybenzyl, N-1-ethyl-N-1-m-tolyl-2-ethyl, 1-benzyl-piperidin-4-yl, 1-methyl-3-phenylpropyl, 2-fluorobenzyl, 3-(trifluoromethyl)benzyl,

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piperonyl, 1-naphthalenemethyl, 3,4-dichlorobenzyl, (R)-(-)-1-cyclohexylethyl, (+/-)-1-(1-naphthyl)ethyl, 4-(trifluoromethoxy)benzyl and 5-guanidinopentanoic acid-2-yl.

5

40. The combinatorial library of claim 39, wherein

Z is the structure A or the structure C, wherein:

- 10 X is carbonyl and the combination of X-R₈ is selected from the group consisting of benzoyl, methoxyacetyl, tert-butylacetyl, 2,4-difluorobenzoyl, 2,4-dimethylbenzoyl, 2-ethylhexanoyl, 2-propylpentanoyl, 3-indolepropionyl, N-phenylanthranilyl, trans-2-carboxycyclohexanoyl, cyclohex-3-en-oyl, trans-pent-2-en-oyl, 1-methyl-1-cyclohexanoyl, 1-acetylpiridine-4-carbonyl, cyclopropanecarbonyl, methanesulfonylacetyle, 5-hexynoyl, 3-furoyl, 3,4-difluorophenylacetyle, 3-benzoyl-benzoyl, 2-(trifluoromethyl)phenylacetyle, 4-(trifluoromethyl)phenylacetyle, 2-acetylmino-3-(1H-indol-3-yl)-propionyl, 3-(phenylsulfonyl)propionyl, 2-benzyloxyphenylacetyle, benzo(b)thiophene-3-acetyl, 3-fluoro-2-methyl-benzoyl, 1-methylcyclopropane-1-carboxyl, (-)-menthoxyacetyl, cyclohexyl-1-acetic acid-1-methylcarbonyl, 2-(3-trifluoromethyl-phenylamino)-benzoyl, 2-ketobutyryl, 2-ethyl-2-hydroxybutyryl, 5-chlorovaleryl, 1-acetyl-pyrrolidine-2-carbonyl, 5-chlorothiophene-2-carboxylyl, 2-(2-methoxyethoxy)acetyl, 2-methyl-3-furoyl, 6-heptynoyl, 5-methylisoxazole-4-carbonyl; or
- 25
- 30

X is sulfonyl and the combination of X-R₈ is selected from the group consisting of 2-mesitylenesulfonyl, 2-naphthenesulfonyl, 2-thiophenesulfonyl, 4-chlorobenzenesulfonyl, 4-fluorobenzenesulfonyl, N-5 acetylsulfanilyl, 2-acetamide-4-methyl-5-thiazolesulfonyl, 4-tert-butylbenzenesulfonyl, 8-quinolinesulfonyl, 3-chloro-4-fluorobenzenesulphonyl, 4-ethylbenzenesulfonyl, pentamethylbenzenesulfonyl, 2,4-dichlorobenzenesulphonyl, 2-chloro-6-methylbenzenesulphonyl, 3,4-10 difluorobenzenesulphonyl, 3,5-dichlorobenzenesulfonyl, 3-chlorobenzenesulfonyl, 3-fluorobenzenesulphonyl, 4-trifluoromethylbenzenesulphonyl, 2-(methoxycarbonyl)thiophene-3-sulfonyl, 1-methylimidazole-4-sulfonyl, 3-chloro-4-methylbenzenesulfonyl, 4-15 isopropylbenzenesulphonyl, 3,4-dichlorobenzenesulfonyl, 1-naphthalenesulfonyl, 3-nitrobenzenesulfonyl, 4-bromobenzenesulfonyl, 4-nitrobenzenesulfonyl, 2,3,5,6-tetramethylbenzenesulfonyl, p-xylene-2-sulfonyl, 4-n-propylbenzenesulfonyl, 4-n-amylbenzenesulfonyl, 20 2-chlorobenzenesulfonyl, 5-chlorothiophene-2-sulfonyl, m-toluenesulfonyl, 2-bromobenzenesulfonyl, p-styrenesulfonyl, 4-pentylbenzene-1-sulfonyl, 4-n-butylbenzenesulfonyl and 2-methylsulfonylbenzenesulfonyl.

25

41. The combinatorial library of claim 40, wherein:

Z is the structure A, wherein:

30 m is 0;

R_5 is selected from the group consisting of 1,4-butylene, 1,2-ethylene and 1,3-propylene;

5 R_6 and R_7 are directly attached and, combined, is 1,2-ethylene; or R_6 and R_7 are not directly attached and are each selected from the group consisting of hydrogen and ethyl.

10 42. The combinatorial library of claim 40, wherein:

Z is the structure A, wherein:

m is 1;

15

n is 3;

R_5 is 1,2-ethylene; and

20 R_6 and R_7 are directly attached and, combined, is 1,2-ethylene.

43. The combinatorial library of claim 40, wherein:

25 Z is structure C, wherein:

K is absent or, if present, is 1,3-propylene.

44. The combinatorial library of claim 39, wherein Z
30 is structure B.

45. The combinatorial library of claim 44, wherein the cyclic portion of structure B is selected from the group consisting of pyrrolidine, piperidine and piperazine.

5

46. The combinatorial library of claim 45, wherein:

the cyclic portion of structure B is selected from the group consisting of 1,2-pyrrolidene, 1,2-piperidene and 10 1,4-piperazene, wherein R₅ is directly connected at the 2-position, 2-position and 4-position, respectively;

15 R₅ is selected from the group consisting of methylene and ethylene; and

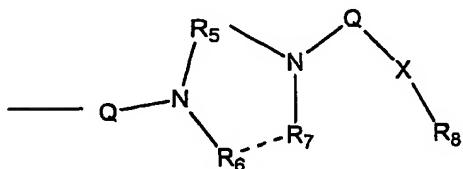
R₈ and R₉ are, independently selected from the group consisting of hydrogen, methyl, ethyl, hydroxyethyl, benzyl, cyclohexyl, isobutyl, propyl, butyl, sec-butyl, hexyl, heptyl, allyl, cyanoethyl, 2-picoly, 20 cyclohexylmethyl, cyclohexylethane-1,1-diyl, N,N-diethylaminoethyl, N,N-dimethylaminopropyl and neopentyl; or

25 R₈ and R₉, together with the adjoining nitrogen atom depicted in structure B are, collectively, selected from the group consisting of pyrrolidin-1-yl, piperidin-1-yl, 3-(carboxamide)piperidin-1-yl, 2-(carboxamide)pyrrolidin-1-yl, 4-(methyl)piperazin-1-yl, morpholin-4-yl, 2-(hydroxymethyl)piperidin-1-yl, 4-30 (ethylcarboxylate)piperidin-1-yl, 4-(phenyl)piperazin-1-yl,

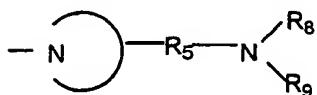
4-(2-pyrimidyl)-piperazin-1-yl, thiomorpholin-4-yl, 4-(benzyl)piperazin-1-yl, 3-(ethylcarboxylate)piperidin-1-yl, 4-(hydroxy)piperidin-1-yl, 3,5-(dimethyl)piperazin-1-yl, homopiperazin-1-yl, 4-(methyl)homopiperazin-1-yl, 2-5 (methyl)piperidin-1-yl, 3,5-(dimethyl)piperidin-1-yl, 3-(N,N-dimethylamino)pyrrolidin-1-yl, 3-(amino)pyrrolidin-1-yl, homopiperidin-1-yl, decahydroquinolin-1-yl and tetrahydroisoquinolin-1-yl.

10 47. A method of making the compound of claim 1, comprising displacing a leaving group on the 2-position of a benzoxazole derivative with a diamine derivative selected from the group consisting of formula A:

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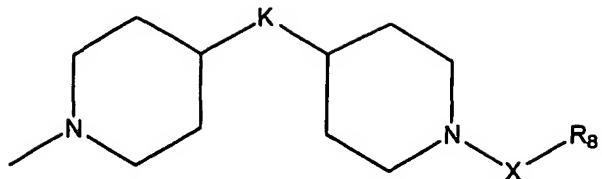


20 formula B:



25

and formula C:



wherein, in formula A, Q is the formula $((\text{CH}_2)_n\text{NH})_m$, where 5 m is 0 or 1, n is 1 to 6 and the alkylene portion of Q is directly attached to the depicted nitrogen atom in formula A; and the dotted line between R_6 and R_7 , which are variable groups, indicates that R_6 and R_7 are optionally directly attached;

10 wherein, in formula B, the depicted cyclic portion is an unsubstituted or substituted heterocycle that is fully saturated, contains 4 to 7 ring atoms, 1 to 2 nitrogen rings atoms and 0 to 1 other heteroatoms selected from 15 oxygen and sulfur, and R_5 , R_8 and R_9 are variable groups;

wherein, in formula C, K is absent or present and, if 20 present, is a C_1 to C_{12} alkylene, X optionally present as a carbonyl, thiocarbonyl, thioester, sulfonyl or sulfinyl group, and R_8 is a variable group.

48. The method of claim 47, wherein $-\text{Q}-\text{X}-\text{R}_8$ of formula A or $-\text{X}-\text{R}_8$ of formula C is attached to the rest of the formula by replacing a hydrogen.

25 49. The method of claim 47, wherein $-\text{N}\text{R}_8\text{R}_9$ of formula B is attached to the rest of the formula by displacing a leaving group.

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50. The method of claim 47, wherein said benzoxazole derivative is attached to resin.

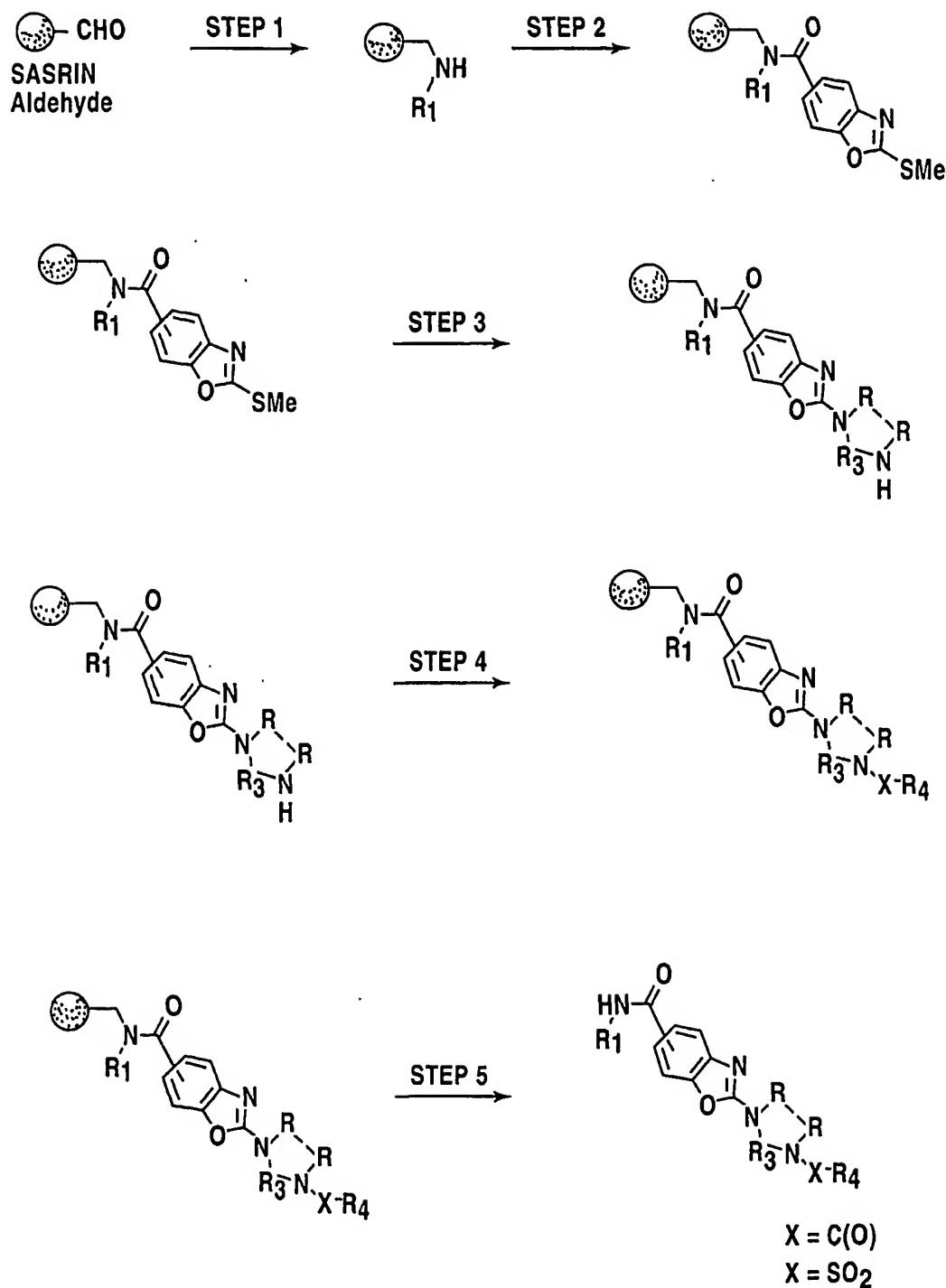
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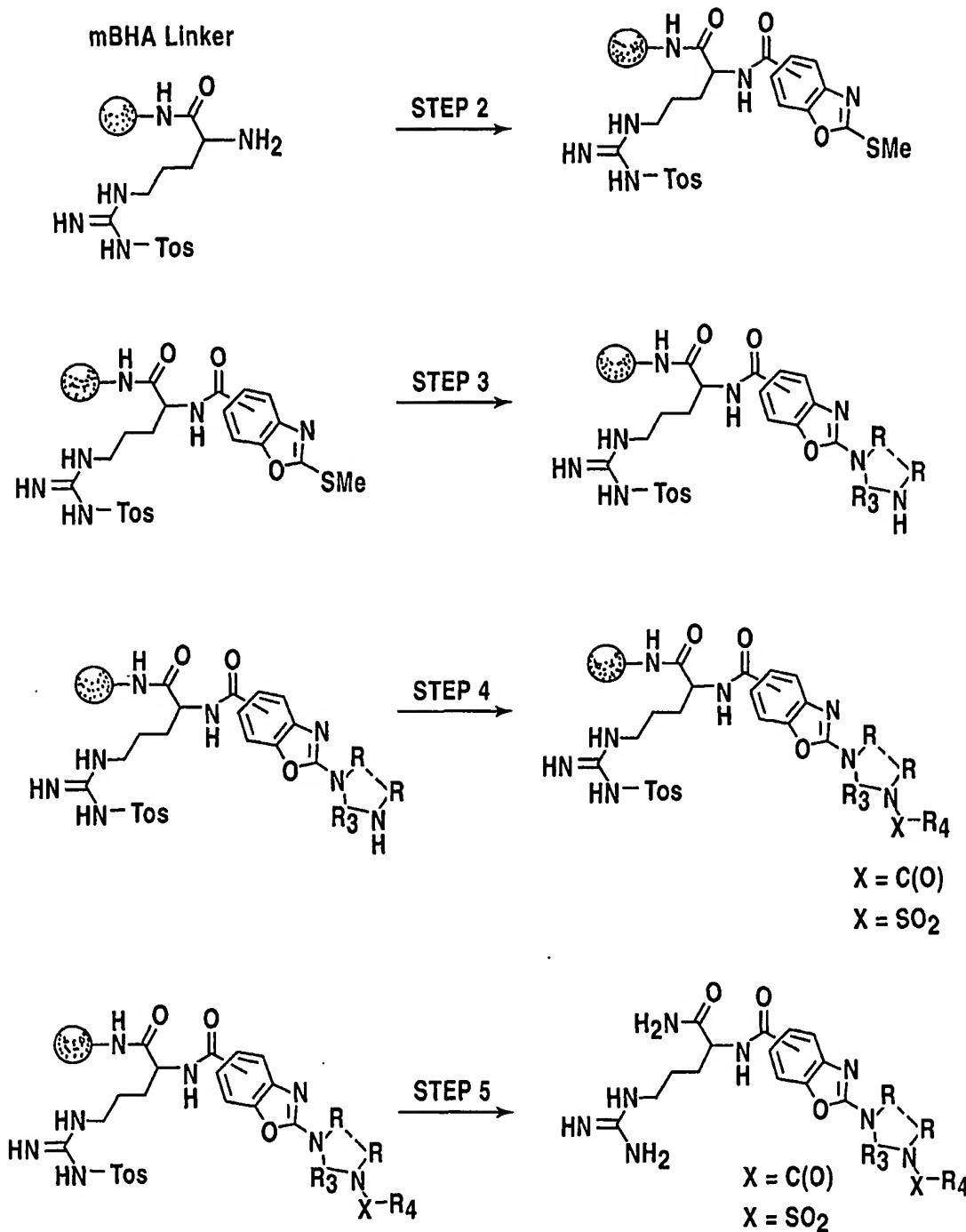
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Fig.1



2/3

Fig.2



3/3

Fig.3

